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Patterns of Care in Medical Oncology

Management of Breast Cancer in the Neoadjuvant, Adjuvant and Metastatic Settings

Survey of 100 Practicing Medical Oncologists on Clinical Scenarios and Patient Cases Presented by Contributing Faculty Members

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OVERVIEW OF ACTIVITY

It is important for medical oncologists, hematologists and fellows to be aware of similarities and differences between their patterns of cancer care and those of other community practitioners. Additionally, the recognition that heterogeneity exists within the treating oncology community underscores the existence of clinical situations for which the research evidence to support a single definitive approach may be suboptimal.

This program focuses on the self-described practice patterns of randomly selected community medical oncologists and hematologists in a variety of key clinical scenarios in breast cancer. Also included are clinical investigator commentaries describing clinical scenario-related treatment selections and management patterns. This CME program provides medical oncologists, hematologists and hematology-oncology fellows with information on national cancer patterns of care to assist with the development of best-practice clinical management strategies for breast cancer.

LEARNING OBJECTIVES

- Compare and contrast management strategies employed by community-based medical oncologists and clinical investigators in the treatment of breast cancer, and use this information to refine or validate practical treatment decision-making.
- Identify clinical scenarios for which relative agreement and heterogeneity exist in patterns of breast cancer care, and apply these findings to the individualized care of patients.
- Counsel patients with breast cancer about the benefits and risks of multiple acceptable evidence-based treatment options when they exist.
- Apply the results of new data with biomarkers and multigene assays to the routine care of patients with breast cancer.
- Explain to patients how breast cancer molecular subtype influences disease prognosis and selection of appropriate systemic treatment.
- Recognize the rate at which practice-changing clinical research influences oncologist behavior, and explain how this affects patient access to standard and novel therapeutics.
- Recall the design and eligibility criteria for ongoing breast cancer clinical trials, and consent or refer appropriate patients for study participation.

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PowerPoint files of the graphics contained in this document can be downloaded at **www.ResearchToPractice.com/POCB111**.

ABOUT THIS SURVEY

This survey was completed in October 2010 by 100 community-based medical oncologists who treat breast cancer in the United States. The community-based oncologists were selected from a proprietary mailing list used by Research To Practice for distribution of its CME programs. Drs Joseph Sparano, Eric Winer and Nicholas Robert contributed to the survey development.

Editor's Note: Chalk talk

The conference room adjoining the oncology inpatient unit where I did my fellowship was always jammed with fellows, residents, nurses and others trying to soak up as much knowledge as possible from faculty mentors. The best days there were when the "attending of the month" would simply write a few intriguing words on the beat-up marker board and then spend the rest of the time using those thoughts to lead an interesting and relevant conversation.

In reading through the reams of data that resulted from our most recent Patterns of Care study I thought about how the findings would make great fodder for one of those informal chats, so I decided to pick out a few and present them as if standing before a room full of disciples at The U a long time ago.

More than a hundred

Fellows in training — should they elect to enter general oncology practice — can expect to provide care for more than 100 different individuals with breast cancer during a typical year (Figure 1). They can also anticipate that approximately one patient per month will die from the disease (Figure 1), and some of these will be women with minor children.

Almost every day

Oncologists deliver more bad news than perhaps any other physician subspecialty, and several times a week or more they must tell one of their patients that their cancer has recurred or progressed (Figure 1).

Approximately a third of these encounters — and indeed about a third of medical oncology practice — focus on women with breast cancer.

Pretty much all oncologists

The very wise professor Hyman Muss has made the point that there is a rapid and efficient means of self-selection in medical oncology, and people who have a hard time dealing with desperate situations or who don't derive a great deal of gratification from this very challenging field make their way to other places.

Our survey documents that most of those who remain on the front lines of cancer patient care adjust relatively well to profound daily stressors (Figure 2) and perhaps as a major source of strength and balance spend a great deal of their available time with family and friends and figure out a way to at least occasionally get away from it all.

In addition to these more global survey findings, we as usual also asked about

FIGURE 1

*In the **past year**...*	
How many different people with breast cancer have you treated for...	
	Median
Metastatic disease	50
Adjuvant therapy	75
Neoadjuvant therapy	12
How many people with breast cancer in your practice died from the disease?	12
How many of these people were mothers of minor children?	2
*In the **past month**...*	
*How many times did you tell a patient with **any type** of cancer that his/her disease was progressing or recurring?*	13
How many of these were people with breast cancer?	4

Survey of 100 US-Based Oncologists, October 2010.

Telling a Patient with Metastatic Breast Cancer That the Disease Is Progressing... Two-Scotch Nights

"As an oncologist, I don't think you ever get used to being in this type of situation, and perhaps if you do, you need to be doing something else. I call these 'two-scotch nights,' and have had a fair amount of them.

It helps to have colleagues and friends reassure you that you've done your best and to empathize with you, but I don't think you ever quite get used to it.

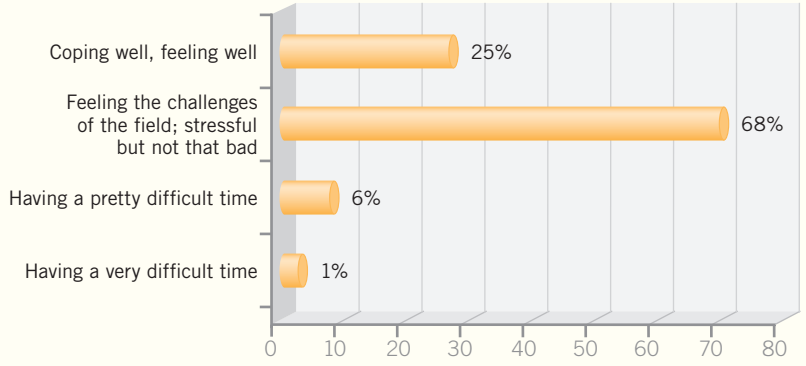
I believe oncologists are a preselected group. If you get into your fellowship and you see these patients and you really can't handle it, you get out. We probably like high-impact medicine and might not be very happy in the dermatology clinic.

We get a lot of sharing and help from our friends, but we never get used to it."

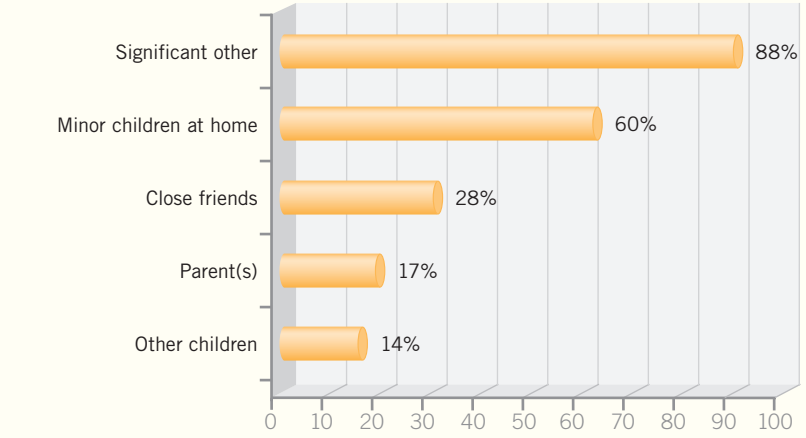
Hyman Muss, MD
***Meet The Professors* Discussion**
2006

FIGURE 2

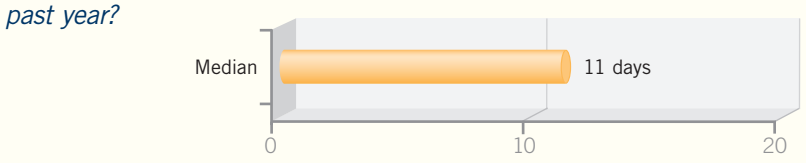
Which of the following best describes how well you cope with the stresses of medical oncology?



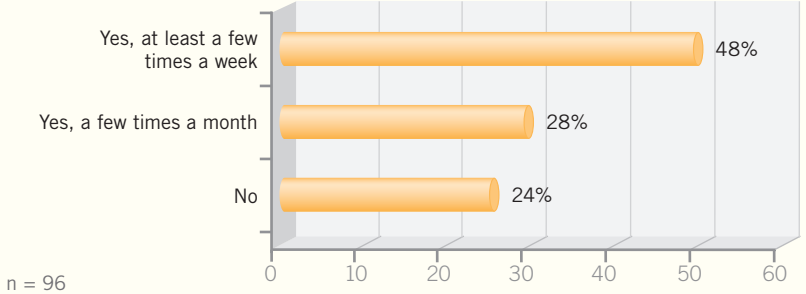
Of your family and close friends, whom do you see daily or very frequently? (May have more than 1 response)



What was the longest vacation/time away from your practice you took in the past year?



Do you engage in any hobbies/sports?



n = 96

very specific practice trends, and here are the ones I would jot on the board.

One in four

As in prior efforts, one of our major goals for this project was to gain a better understanding of how genomic biomarkers are integrated into practice. More specifically, the coeditors, Drs Eric Winer and Joe Sparano (featured on the enclosed audio CD), and I decided to explore a new aspect of a common clinical scenario — a patient with a node-negative, ER-positive, HER2-negative tumor.

We know from prior surveys that most of these patients will have their tumors tested using the Oncotype DX® assay, but the question we wanted to ask was, do oncologists use the Recurrence Score® not only to determine *whether* to give chemo, but also *what type* of chemo to administer.

The answer is that about 25 percent of physicians base their chemo regimen selection on Oncotype DX findings (Figure 3, page 5). Presumably the thinking is that for a high Recurrence Score (and maybe a larger tumor and worse grade) one might use an anthracycline followed by a taxane, whereas for a patient with an intermediate score — where the issue of *whether* or not to use chemo is on the table — the choice might be something like TC (docetaxel/cyclophosphamide).

Many investigators don't agree with this practice, but at a recent Think Tank the NSABP's Chuck Geyer defended this approach, noting that he feels less confident in the benefit of endocrine treatment in patients with high Recurrence Scores and that to him it makes sense to use more chemotherapy when there is potential for greater reduction of recurrence risk.

Almost all

One of the more intriguing and oft-debated issues in breast cancer is adjuvant treatment for older patients with tumors carrying a poor short-term outlook. At the top of that list is node-

positive, HER2-positive breast cancer, and for an otherwise healthy 85-year-old woman, 96 percent of oncologists would use trastuzumab monotherapy (30 percent), chemo or both (Figure 35, page 27). The likely thought process is that even if this approach doesn't alter overall survival, it may avoid the morbidity of shorter-term recurrence.

More than half

The management of T1a-bN0 HER2-positive tumors has been hotly debated since the initial presentation of the adjuvant trastuzumab trials at ASCO in 2005, and for a variety of complex reasons, investigators have usually drawn the line at 0.5 centimeters and will not use trastuzumab or chemo for smaller tumors.

In this survey, for the first time we observed that a substantial fraction of respondents (58 percent) would use chemo/trastuzumab for a patient with a 0.3-cm, ER-negative, HER2-positive, node-negative tumor (Figure 36, page 28).

About a quarter

There are relatively minimal data available to guide the clinical use of genomic assays in the *neoadjuvant* setting, but this survey demonstrates that 28 percent of oncologists are using Onco*type* DX before surgery (Figure 8, page 7). Most investigators also state that they don't employ this strategy outside a trial setting. However, I wonder why not.

It seems logical that — for example — the possibility of tumor shrinkage to facilitate breast conservation would be greater with endocrine treatment as opposed to chemo in patients with low Recurrence Score tumors.

I also wonder why we don't consider some measure of quantitative ER and proliferation like Onco*type* DX in deciding between a chemotherapy-based treatment plan and an endocrine approach in *metastatic* disease, particularly if the patient is symptomatic.

About three quarters

We found that 74 percent of oncologists would order a biopsy for a 60-year-old patient with suspected lung and bone metastases two years after completion of dose-dense adjuvant chemotherapy for node-positive, triple-negative breast cancer (Figure 25, page 19).

Given the San Antonio report from Sweden demonstrating that approximately a third of biopsied mets have an ER and/or HER2 result different than the primary tumor, one might argue that the most important action one could take for such a patient would be rebiopsy.

After all, with triple-negative disease, a shift toward positive for either ER or HER2 (or finding something other than metastatic breast cancer) would be a relatively good thing.

About three quarters

The landmark German trial first reported at ASCO a couple of years ago supported the utility of continuous HER2 blockade in the metastatic setting and validated the strategy in select situations in metastatic HER2-positive disease of continuing trastuzumab and changing the partnering chemotherapy agent.

But what about patients who develop disease relapse after prior adjuvant trastuzumab, for whom another HER2 option is lapatinib?

Perhaps considering the greater risk of bothersome side effects with the TKI — and mindful of related data from studies like the German trial — oncologists are more commonly turning to trastuzumab than lapatinib, with 78 percent of those surveyed selecting to administer trastuzumab alone or in combination to patients whose disease has relapsed 18 months after the completion of trastuzumab-containing adjuvant therapy (Figure 40, page 32).

A bit more than a third of oncologists (35 percent) would make this same treatment selection for relapsed disease as early as six months after the completion of adjuvant trastuzumab.

About half

When asked which treatment they would generally offer a 60-year-old patient with symptomatic triple-negative metastatic disease, 48 percent of respondents stated they would recommend a taxane and bevacizumab (Figure 26, page 20). The current intense deliberation and drama playing out at the FDA will determine whether these physicians will be able to use their preferred treatment in the near future.

About half

One of the most dramatic shifts documented by this long series of surveys relates to the selection of endocrine treatment in metastatic disease, particularly when the patient experiences disease relapse while receiving an adjuvant AI.

In prior assessments, physicians pretty much chose equally among tamoxifen, fulvestrant and the steroidal AI exemestane, but in this study there was a major shift, with 47 percent opting for fulvestrant and the next choice at 27 percent being exemestane (Figure 12, page 10).

This change likely reflects new thinking based on relatively recent data that if the increased 500-mg monthly dose of fulvestrant seems to be more effective than anastrozole and anastrozole is about the same as exemestane, then fulvestrant might be the best available option.

Much of what we know about the management of breast cancer is shaped and discovered in the labs, clinics and classrooms of ivory tower academic institutions. But the truth is, there is much to be learned from what happens in the solo practices, oncology offices and community hospitals around the country. That's why we conduct these surveys every year, send this monograph to everyone from first-year fellows to the president of ASCO and post it online for all to peruse.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
April 13, 2011

FIGURE 3

Clinical Scenario 1: *A **60-year-old woman** has a 1.0-cm, ER-positive, HER2-negative, node-negative IDC (3 sentinel nodes).*

Would you order an Oncotype DX assay for this patient?

*If **yes** (n = 82), which adjuvant chemotherapy, if any, would you recommend given the following Recurrence Score (RS)?*

Oncotype DX RS	AC → taxane	TC	AC	Other	None
High RS	30%	60%	6%	4%	0%
Intermediate RS	7%	62%	4%	1%	26%
Low RS	0%	4%	0%	3%	93%

*If **no** (n = 18), which adjuvant chemotherapy, if any, would you recommend?*

No Oncotype DX RS	AC → taxane	TC	AC	Other	None
	0%	6%	0%	6%	88%

FIGURE 4

Clinical Scenario 2: *A **75-year-old woman** has a 1.0-cm, ER-positive, HER2-negative, node-negative IDC (3 sentinel nodes).*

Would you order an Oncotype DX assay for this patient?

*If **yes** (n = 46), which adjuvant chemotherapy, if any, would you recommend given the following RS?*

Oncotype DX RS	AC → taxane	TC	AC	Other	None
High RS	22%	63%	11%	2%	2%
Intermediate RS	3%	37%	4%	4%	52%
Low RS	0%	4%	0%	2%	94%

*If **no** (n = 54), which adjuvant chemotherapy, if any, would you recommend?*

No Oncotype DX RS	AC → taxane	TC	AC	Other	None
	0%	11%	0%	4%	85%

Oncotype DX RS and adjuvant chemotherapy selection for ER-positive, node-negative BC

DR JOSEPH SPARANO: The Oncotype DX assay Recurrence Score (RS) has been widely integrated into the decision-making process for adjuvant systemic therapy for patients with ER-positive, node-negative breast cancer. Therefore, it makes sense that in community practice clinicians are using the Oncotype DX assay more often to aid in adjuvant therapy selection for a younger patient versus an older patient.

For a younger patient, such as this 60-year-old described in Clinical Scenario 1 (Figure 3), who is borderline in terms of meeting established criteria for recommending adjuvant chemotherapy, Oncotype DX is ordered more for treatment-sparing purposes.

For an older patient, such as the 75-year-old described in the second clinical scenario (Figure 4), chemotherapy would not normally be recommended. Oncotype DX would be ordered for treatment selection instead of for treatment-sparing purposes. These data mirror what I would do in my own clinical practice. I would definitely order the Oncotype DX assay for a patient resembling the one in Clinical Scenario 1 and would not order it for a patient similar to the one in Clinical Scenario 2.

A gray zone exists between the ages of 60 and 70 in terms of what therapy to select. The Oncotype DX RS does affect my treatment selection for a patient. CMF is the regimen that would normally be recommended. I would not use CMF for patients who have an intermediate or midrange RS to whom I have decided to administer chemotherapy. I would use an alternative regimen such as AC or TC. If the patient has positive lymph nodes or micrometastases, I would select a more aggressive sequential regimen.

The other factor that goes into the decision about whether to order Oncotype DX is tumor grade. If the patient has an intermediate-grade tumor,

FIGURE 5

Clinical Scenario 3: *A 60-year-old woman has a* ***3.4-cm****, ER-positive, HER2-negative, node-negative IDC (3 sentinel nodes).*

Would you order an Oncotype DX assay for this patient?

If ***yes*** *(n = 64), which adjuvant chemotherapy, if any, would you recommend given the following RS?*

Oncotype DX RS	AC → taxane	TC	AC	Other	None
High RS	38%	53%	6%	2%	2%
Intermediate RS	11%	72%	6%	2%	9%
Low RS	3%	11%	2%	2%	82%

If ***no*** *(n = 36), which adjuvant chemotherapy, if any, would you recommend?*

No Oncotype DX RS	AC → taxane	TC	AC	Other	None
	33%	42%	11%	6%	8%

FIGURE 6

Clinical Scenario 4: *A* ***75-year-old woman*** *has a 3.4-cm, ER-positive, HER2-negative, node-negative IDC (3 sentinel nodes).*

Would you order an Oncotype DX assay for this patient?

If ***yes*** *(n = 61), which adjuvant chemotherapy, if any, would you recommend given the following RS?*

Oncotype DX RS	AC → taxane	TC	AC	Other	None
High RS	16%	69%	5%	7%	3%
Intermediate RS	3%	46%	3%	5%	43%
Low RS	2%	6%	2%	5%	85%

If ***no*** *(n = 39), which adjuvant chemotherapy, if any, would you recommend?*

No Oncotype DX RS	AC → taxane	TC	AC	Other	None
	5%	41%	5%	13%	36%

then you are in more of an equipoise situation and Oncotype DX can be helpful in terms of pointing toward one direction or another. If the patient has a poor-grade tumor, the chance of the Oncotype DX RS being low is approximately 20 percent. If you are being pushed in the direction of chemotherapy on the basis of clinical characteristics, obtaining a low Oncotype DX RS could prevent you from choosing chemotherapy. I believe, though, that you need to be comfortable with the pathology lab that is reporting the tumor grades because the reading of tumor grades can vary from laboratory to laboratory.

DR ERIC WINER: For this particular woman in Clinical Scenario 1 (Figure 3), who's 60 and has a T1bN0 tumor, I would likely not administer a combination of an anthracycline and a taxane. Generally speaking, I don't order an Oncotype DX assay to guide my chemotherapy choice and I don't know that the Oncotype DX should guide us in terms of which chemotherapy we administer.

On some level, however, one could rationally argue that Oncotype DX should be used for that purpose because a patient with a high Oncotype DX RS has a higher risk of recurrence compared to someone with an intermediate RS. Potentially more can be gained for this patient with a more complex chemotherapy regimen than with a simpler regimen such as TC or AC.

The other piece of information that I would want to have is tumor grade. If a patient was 60 years old and had a Grade I, 1-cm tumor, I would not order an Oncotype DX assay. The problem with grade — and in many ways, this is what makes Oncotype DX a little easier to interpret — is that grade is highly variable across pathologists.

Many of us find grade useful when we have a consistent pathologist or consistent pathology group interpreting it, but it is often difficult to know what to make of grade from an outside institution or from a pathologist with whom you do not have a relationship.

FIGURE 7

Clinical Scenario 5: *A 60-year-old woman has a core biopsy of a* ***4-cm****, ER-positive, HER2-negative, node-negative IDC (3 sentinel nodes). The patient wishes to undergo breast-conserving surgery, which will be difficult or impossible without shrinkage of the breast mass, so* ***neoadjuvant therapy*** *is being considered.*

Would you generally order the Oncotype DX assay for this patient?

Which of the following neoadjuvant regimens, if any, would you most likely recommend for this patient?

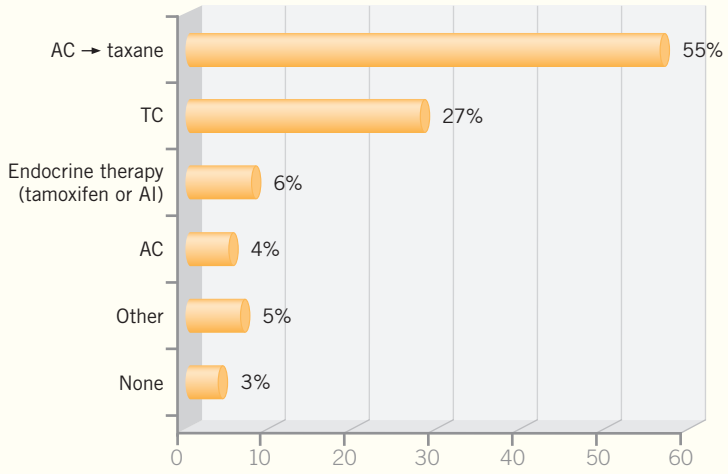


FIGURE 8

Have you ordered the Oncotype DX assay to assist with decision-making regarding neoadjuvant therapy?

Median number of assays ordered: 5

Oncotype DX RS and neoadjuvant therapy for ER-positive, node-negative disease

DR SPARANO: I am not using Oncotype DX in the neoadjuvant setting, but one can make a cogent argument to adopt that approach. Clearly the pathologic complete response (pCR) rates in ER-positive disease are substantially lower than in triple-negative disease using chemotherapy alone or in HER2-positive disease using chemotherapy in combination with trastuzumab.

One could use Oncotype DX to identify those patients with ER-positive disease who are much less likely to experience a pCR — presumably those with a low Oncotype DX RS — and then take an alternative approach for them, which could include proceeding directly to surgery. Or it could include treating with neoadjuvant endocrine therapy. I believe that is how the use of Oncotype DX in the neoadjuvant setting may be useful. I do not believe that it should be done in routine clinical practice, but it's an approach that's being evaluated now in prospective trials.

DR WINER: I haven't ordered Oncotype DX in the neoadjuvant setting. I've administered preoperative hormonal therapy instead of chemotherapy, largely to postmenopausal women who have ER-positive and typically relatively low-grade disease. I would not usually follow that course for somebody who has a poorly differentiated tumor, but I would for a patient with a well- to moderately differentiated tumor.

At our institution we still administer AC with some frequency. CMF remains a reasonable regimen, although its main drawback is that it is a long and cumbersome regimen. I believe TC is also a fine regimen to use, and I am interested in seeing more data in the way of TC in different subgroups of patients.

Oncotype DX RS and adjuvant chemotherapy selection for ER-positive, node-positive BC

DR WINER: I'm comfortable ordering Oncotype DX for the 60-year-old woman with two positive lymph nodes in Clinical Scenario 6 (Figure 9). It is extremely unlikely that Oncotype DX will give us fundamentally different information in patients with node-positive versus node-negative disease. Although it is a single trial, the experience in Kathy Albain's SWOG trial made us all feel a little more comfortable using Oncotype DX for patients with node-positive disease.

For the 75-year-old in Clinical Scenario 7 (Figure 9), I would not order an Oncotype DX assay because I believe it is unlikely that a 75-year-old woman with estrogen receptor-positive breast

FIGURE 9

Clinical Scenario 6: *A 60-year-old woman has a* ***1.0-cm****, ER-positive, HER2-negative IDC with* ***2 positive nodes****.*

Would you order an Oncotype DX assay for this patient?

If ***yes*** *(n = 24), which adjuvant chemotherapy, if any, would you recommend given the following RS?*

Oncotype DX RS	AC → taxane	TC	AC	Other	None
High RS	38%	50%	4%	4%	4%
Intermediate RS	29%	58%	0%	0%	13%
Low RS	8%	8%	4%	4%	76%

If ***no*** *(n = 76), which adjuvant chemotherapy, if any, would you recommend?*

No Oncotype DX RS	AC → taxane	TC	AC	Other	None
	58%	24%	7%	6%	5%

Clinical Scenario 7: *A* ***75-year-old*** *woman has a 1.0-cm, ER-positive, HER2-negative IDC with 2 positive nodes.*

Would you order an Oncotype DX assay for this patient?

If ***yes*** *(n = 44), which adjuvant chemotherapy, if any, would you recommend given the following RS?*

Oncotype DX RS	AC → taxane	TC	AC	Other	None
High RS	25%	57%	5%	11%	2%
Intermediate RS	11%	50%	0%	9%	30%
Low RS	0%	12%	2%	2%	84%

If ***no*** *(n = 56), which adjuvant chemotherapy, if any, would you recommend?*

No Oncotype DX RS	AC → taxane	TC	AC	Other	None
	32%	34%	7%	9%	18%

cancer for whom I would be anxious to recommend chemotherapy exists.

If you consult Adjuvant! Online, a woman with node-positive, ER-positive disease will obtain an extraordinarily small benefit from chemotherapy at age 75. Although not the norm, for the 75-year-old who has absolutely no comorbidities, has a high-grade tumor and has an Oncotype DX RS that would support the fact that this patient would likely benefit more from chemotherapy, then I would consider it.

One should remember that with ER-positive breast cancer, deaths from breast cancer are distributed over the course of not five years or eight years, but over 20 to 25 years at a minimum. Chemotherapy, for the most part, only prevents early recurrences. A 75-year-old woman with ER-positive breast cancer will experience risk of recurrence that is unlikely to be affected by chemotherapy.

DR SPARANO: For an older patient such as this 75-year-old with positive nodes described in Clinical Scenario 7 (Figure 9), I absolutely would consider chemotherapy. That would be a situation in which I believe Oncotype DX would be helpful in terms of the use of sparing chemotherapy.

Oncotype DX has been validated in two randomized trials in which patients with ER-positive disease were randomly assigned to receive either endocrine therapy alone or endocrine therapy in combination with chemotherapy. The results were consistent in both of those trials in that only patients who had a high Oncotype DX RS seemed to benefit from chemotherapy.

The SWOG-8814 study included patients with one to three and more than three positive nodes. In both groups of patients a relationship seemed to exist between higher Oncotype DX RS and benefit from chemotherapy.

However, the absolute risk of recurrence was higher in patients who had four or more positive nodes versus those who had one to three positive nodes. Nodal status is prognostic but not necessarily predictive of the benefit from chemotherapy, whereas the Oncotype DX RS is both prognostic and predictive. Oncotype DX can add complementary information to the nodal status and can help one make a treatment decision.

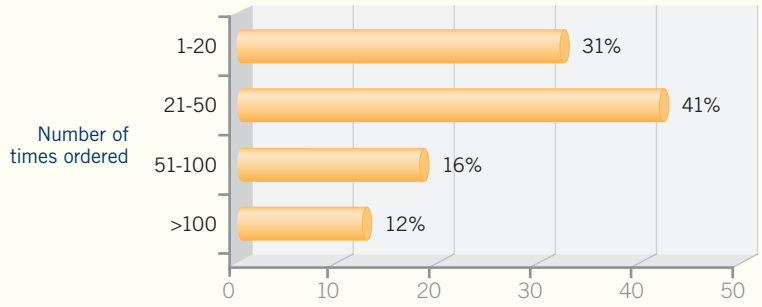
FIGURE 10

Have you ordered the Oncotype DX assay for a patient with node-positive disease?

Median number of assays ordered: 5

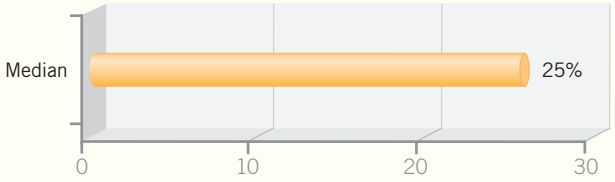
FIGURE 11

During your career, approximately how many times have you ordered the Oncotype DX assay?



Median number of assays ordered: 40

What percent of the time did the Oncotype DX results cause you to alter your preconceived treatment recommendation?



The issue becomes the level of evidence supporting a decision to spare chemotherapy in someone for whom you would normally have recommended chemotherapy. Currently, we're not basing these decisions on a tremendous amount of evidence and it would be reassuring to see more.

The SWOG-S1007 trial is evaluating RS and Oncotype DX in patients with node-positive tumors. Patients with one to three positive nodes who have ER-positive, HER2-negative disease will be eligible, and Oncotype DX assays will be performed. If the RS is greater than 25, patients will be advised to receive chemotherapy off protocol or be offered other clinical trials. If their RS is 25 or less, patients will be randomly assigned to receive chemotherapy and endocrine therapy or endocrine therapy alone.

With regard to the MammaPrint® assay, data indicate that patients who have positive lymph nodes and good-risk MammaPrint signatures are not likely to benefit from chemotherapy. The validation studies, however, whether they be the original validation studies or the external validation studies, have not been conducted in patients who were randomly assigned to receive endocrine therapy or endocrine therapy in combination with chemotherapy.

I don't believe we have as much information about the predictive value of MammaPrint as we do for Oncotype DX. However, because both assays are largely driven by their ability to measure the proliferative capacity of cancer cells, which drives responsiveness to chemotherapy, one can speculate that the two assays are likely to be roughly concordant in their ability to predict benefit from chemotherapy.

Clinical use of Oncotype DX

DR SPARANO: How often you use the Oncotype DX assay depends on the type of practice you have. If you have a university-based practice where you tend to see younger patients and referrals, you would order the test more often than in a more typical community-based practice in which the median age of your patients is 65 to 70.

SELECT PUBLICATIONS

Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial.** *Lancet Oncol* 2010;11(1):55-65.

Dowsett M et al. **Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal breast cancer patients treated with anastrozole or tamoxifen: A TransATAC study.** *J Clin Oncol* 2010;28(11):1829-34.

Hornberger J et al. **Meta-analysis of the decision impact of the 21-gene breast cancer Recurrence Score in clinical practice.** San Antonio Breast Cancer Symposium 2010;**Abstract P2-09-06**.

Lo SS et al. **Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection.** *J Clin Oncol* 2010;28(10):1671-6.

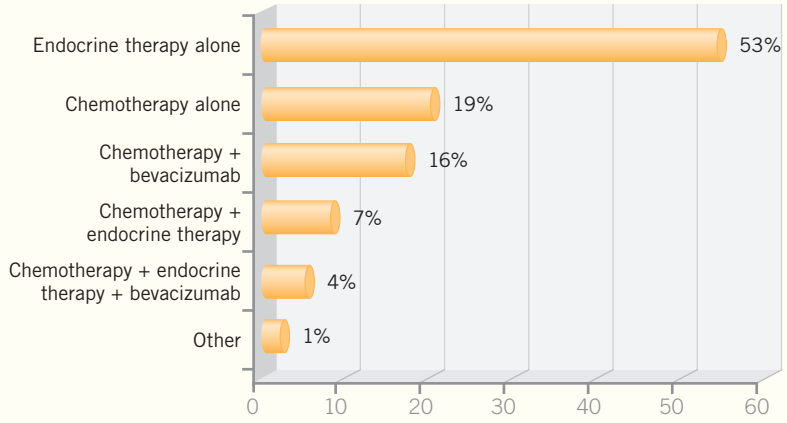
Paik S et al. **A multigene assay to predict recurrence of tamoxifen treated node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

Sparano JA, Paik S. **Development of the 21-gene assay and its application in clinical practice and clinical trials.** *J Clin Oncol* 2008;26(5):721-8.

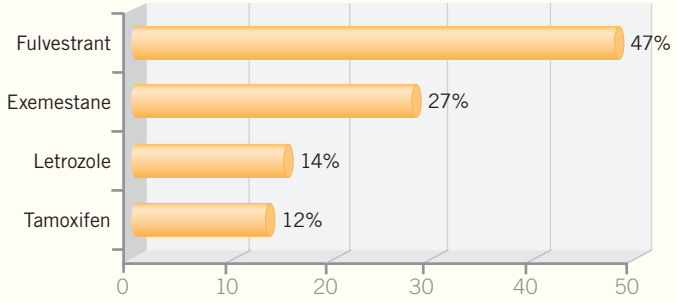
FIGURE 12

Clinical Scenario 8: *A **60-year-old** postmenopausal woman received dose-dense AC → paclitaxel 2 years ago followed by anastrozole for a 2.1-cm, **ER/PR-positive, HER2-negative** IDC with 3 positive nodes. While still receiving anastrozole, she now presents with asymptomatic pulmonary nodules and multiple hot spots on bone scan. Lung biopsy is consistent with the primary tumor.*

Which of the following systemic treatments, if any, would you most likely recommend for this patient?



Which endocrine therapy regimen would you recommend?



n = 51

Endocrine therapy for HER2-negative metastatic disease

DR SPARANO: My default position would be to use endocrine therapy whenever possible for a patient who has ER-positive metastatic disease, including for patients who have disease that has become resistant to prior endocrine therapies, either because they experience disease progression while receiving an endocrine regimen for metastatic disease or have experienced relapse while receiving adjuvant endocrine therapy.

The first critical point is whether chemotherapy is indicated, and that would depend largely on the patient's symptomatology, disease burden and disease-free interval. Greater symptoms, higher disease burden and shorter disease-free interval would push in the direction of chemotherapy, especially if we're dealing with a younger patient.

In terms of the type of endocrine therapy to use if the decision was to use endocrine therapy alone, if the patient has experienced relapse while not receiving endocrine therapy and she is postmenopausal, aromatase inhibitors (AIs) would be an appropriate choice. If her disease recurs while she is receiving an AI or she experiences disease progression on an AI, if that AI were a nonsteroidal AI, the options would be switching to either a steroidal AI, such as exemestane, or to fulvestrant. Those two options were shown to be roughly comparable in the EFECT trial.

DR WINER: It's interesting that the most common endocrine agent choice was fulvestrant. I don't know that I can explain that, other than mentioning that clinicians may be a little more enthusiastic about fulvestrant because the trial of double dose versus standard dose showed a small advantage. But I believe this is a situation in which one could legitimately use exemestane or even tamoxifen, which was essentially equivalent in a randomized trial against fulvestrant — albeit not in patients who had experienced disease progression on an AI.

If anything, tamoxifen might have been a bit superior in certain measures. I believe fulvestrant is fine in this situation, but it's interesting that it's administered almost twice as often as exemestane in this survey.

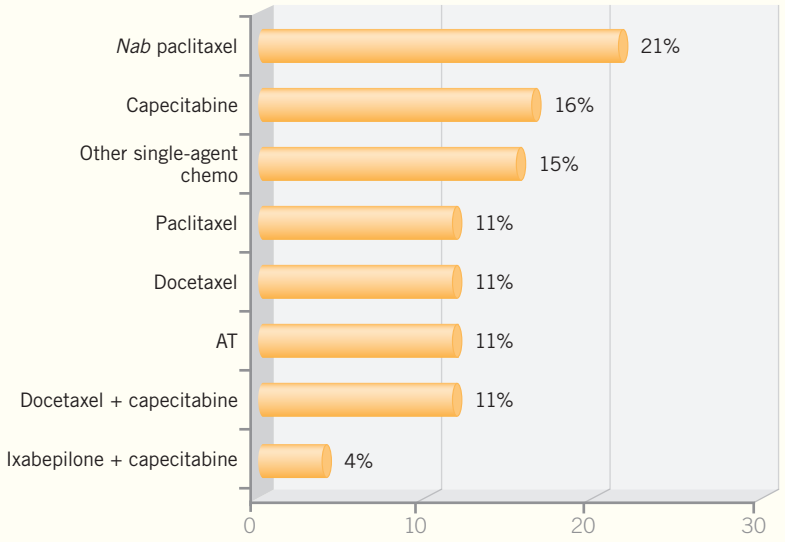
Interview February 3, 2011

DR ADAM BRUFSKY: Generally, if I am still considering combination chemotherapy — for example, two cytotoxic agents together — I believe it's reasonable to also consider a cytotoxic and bevacizumab.

But the kind of patient I probably wouldn't administer this regimen to is someone who has slowly progressive ER-positive breast cancer with a long disease-free interval before she developed metastatic disease. For someone who doesn't

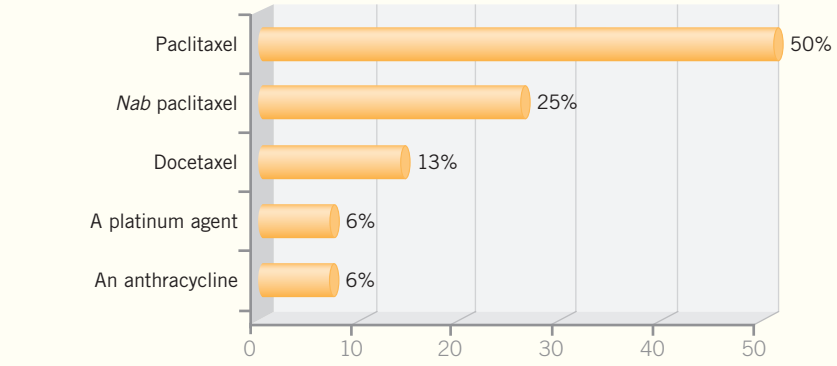
FIGURE 13

For the patient described in Clinical Scenario 8 (Figure 12), which chemotherapy regimen would you recommend?



n = 19

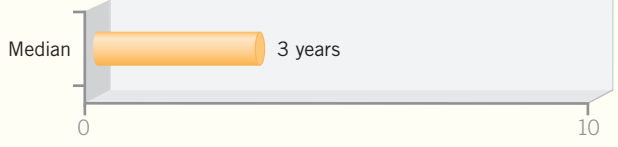
If you were to recommend bevacizumab, which chemotherapy would you combine it with?



n = 16

FIGURE 14

If 100 similar patients were followed in your practice, what would you estimate these patients' median survival to be?



have a lot of cancer — for example, a 65- to 68-year-old woman with a few bony metastatic lesions whose disease has progressed through one, two or three hormone therapies — if I am considering chemotherapy, I probably wouldn't use chemotherapy with bevacizumab.

I would probably use capecitabine, and let me talk about dose with this agent for a moment.

Interestingly, I believe we all use different doses, but we all believe the labeled dose is too high. Many of us will begin by administering three to four pills, 500-mg tablets, BID. That works out to approximately a little less than 2 g/m^2 per day. But I believe many of us are also beginning to use the alternative schedule that was popularized in an abstract by investigators at Memorial Sloan-Kettering, in which you administer one week on, one week off. I've started to use that quite a bit in my practice.

But for a patient with bulkier disease requiring combination chemotherapy, our first line right now is paclitaxel/bevacizumab. If steroids are not indicated for whatever reason, including diabetes, it's nanoparticle paclitaxel/bevacizumab. If someone can only come in every three weeks for therapy, it's docetaxel with or without bevacizumab.

Interview February 3, 2011

DR MELODY COBLEIGH: If I had a patient with metastatic breast cancer who had limited disease and a good performance status to whom I was going to administer chemotherapy, I'd probably administer capecitabine first. When her disease progressed, I would go to paclitaxel and bevacizumab.

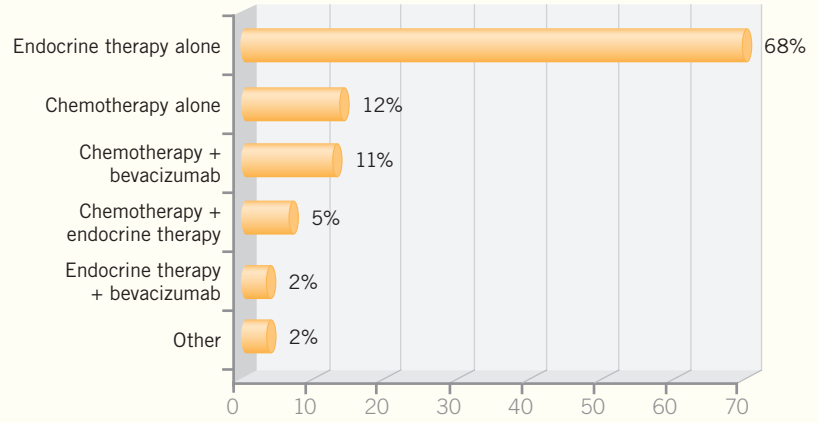
Breast Cancer Update
Issue 1, 2011

DR NICHOLAS ROBERT: Unlike other solid tumors in the metastatic setting, it is interesting how long patients can live with metastatic breast cancer. I'm not sure how well accepted this is throughout the oncology community, but in the breast cancer community, if you have agents that are well tolerated — and I guess the key words are "well tolerated"

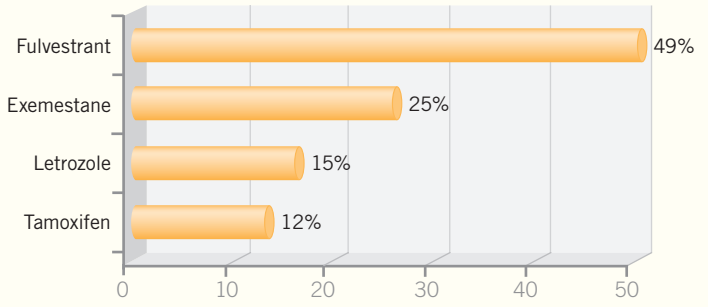
FIGURE 15

Clinical Scenario 9: *A **75-year-old** woman received dose-dense AC → T 2 years ago followed by anastrozole for a 2.1-cm, **ER/PR-positive, HER2-negative** IDC with 3 positive nodes. While still receiving anastrozole, she now presents with asymptomatic pulmonary nodules and multiple hot spots on bone scan. Lung biopsy is consistent with the primary tumor.*

Which of the following systemic treatments, if any, would you most likely recommend for this patient?



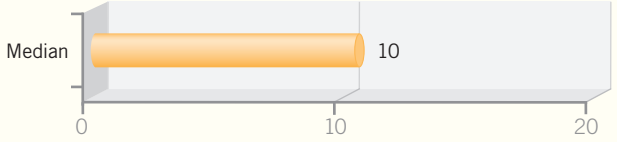
Which endocrine therapy regimen would you recommend?



n = 68

FIGURE 16

For approximately how many patients have you used fulvestrant in the past year?



— and you can prolong survival by a few months, you can line these regimens up one after another and keep someone alive with a good quality of life for a number of months or even years.

It is difficult to prove that, but if you consider registry data — and British Columbia and MD Anderson have such data — you do see a prolongation of life and better survival in patients today compared to those a couple decades ago.

The challenge, of course, is to determine which regimens to administer at which time and how much toxicity is acceptable. And this is like other aspects of oncology — a real art in terms of how to balance the intervention with the patient's quality of life.

Breast Cancer Update
Issue 4, 2010

DR KATHY MILLER: I believe the perception persists that if a patient has any visceral disease, particularly liver involvement, that patient will need chemotherapy. But if you review the literature, you find that the response rates to endocrine therapy of tumors that are hormone sensitive in the liver are just as good as the response rates elsewhere. So I'm trying to get the message out that the liver and lungs don't necessarily need to have such a special place of fear in our minds and that the treatment most likely to help someone is probably biologically based, regardless of the anatomy.

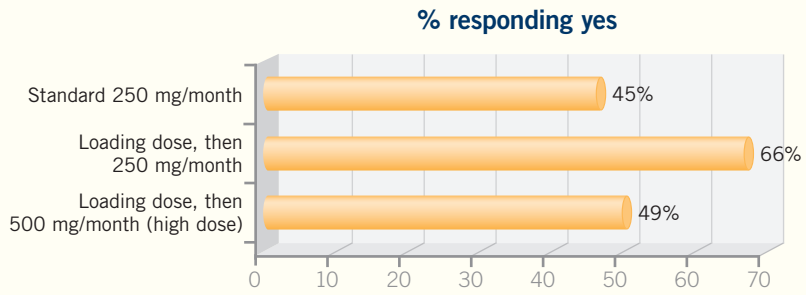
So for someone who is entirely asymptomatic with an incidental finding of liver metastases, I would administer hormone therapy. If her disease doesn't respond to hormone therapy, we still would have ample time to move to chemotherapy with the same expectation of benefit.

Breast Cancer Update
Issue 1, 2011

DR SANDRA SWAIN: I use the 500-mg dose of fulvestrant, and I have for a while because I believe what Kent Osborne has always said — the 250-mg dose was too low. So I have used 500 mg because I believe that's the right thing to do and I believe it's quite active. The FIRST

FIGURE 17

In the past year, have you used the following dosing options for fulvestrant?



study does show that it's an effective drug and that we should be using it more than we do.

Breast Cancer Update
Think Tank 2011

DR WILLIAM GRADISHAR: Fulvestrant has been pushed toward the end of the algorithm for endocrine therapy. Yet it's always been recognized that the 250-mg dose was probably at the lower limit of where you would expect a clinical response. The concern, of course, was that putting a larger amount of viscous material into somebody's buttock might cause discomfort.

But studies have shown, both preclinically and then clinically, that as you escalate the dose or give an increased front-end or loading dose, you not only reach steady-state levels more quickly, but you have a greater likelihood of response, a greater depression of ER, a larger decrease in Ki-67, et cetera.

The FIRST trial was recently updated by John Robertson and compared a higher dose of fulvestrant, 500 mg, to front-line anastrozole in the metastatic setting. The 500 mg of fulvestrant was significantly better in terms of time to disease progression — it was almost doubling the time to disease progression.

Based on those randomized Phase II data, I don't believe it's sufficient to say that fulvestrant should be the standard first-line therapy in the metastatic disease setting, but it does raise the issue of whether we can use a higher dose and get more of a bang with this agent than we had in the past. And I believe fulvestrant could be legitimately considered as a first-line treatment.

Currently, we would use 500 mg. I believe all the data now support the idea of using a higher dose, and the FDA has considered that and changed the recommendations for its use.

Breast Cancer Update
Issue 1, 2011

DR ROBERT: A well-designed prospective trial evaluating a higher dose of fulvestrant — 500 mg administered on day one, day 14, day 28 and then subsequently on an every 28-day schedule — demonstrated a better outcome than that of the standard 250-mg dose. At San Antonio this year, another trial compared this higher dose to an AI in the first-line setting and showed that it has a better progression-free survival (PFS).

So in our practice it's now embedded in our electronic medical records to use the new schedule. I believe that now when we have patients who experience disease progression while receiving an AI, regardless of whether it's steroidal or nonsteroidal, my next step will be to use fulvestrant with the new high-dose schedule.

Breast Cancer Update
Issue 1, 2010

PROF JOHN ROBERTSON: We have data from three consecutive studies — FACT, FIRST and CONFIRM — that I believe provide support for further development of fulvestrant. In 2008 we presented initial data from the randomized Phase II FIRST study, which evaluated fulvestrant 500 mg monthly with a 500-mg loading dose on day 14 of the first cycle versus anastrozole as first-line treatment for advanced breast cancer, showing fulvestrant to be better.

CONFIRM was a Phase III trial comparing fulvestrant 250 mg monthly to 500 mg monthly with a loading dose in more than 700 patients. They could have experienced disease progression in the adjuvant or advanced setting, and roughly 50 percent had previously received an AI. The other 50 percent had received an antiestrogen agent. That's an important point because the results appear to be equally applicable to both subgroups.

The data showed a highly significant difference in PFS favoring the high-dose strategy. I can't recall another second-line Phase III randomized study of an endocrine therapy compared to the standard in which we saw a significant difference in PFS in the first analysis. They also observed that the survival curves start to separate, although they're not significant. That too is unusual.

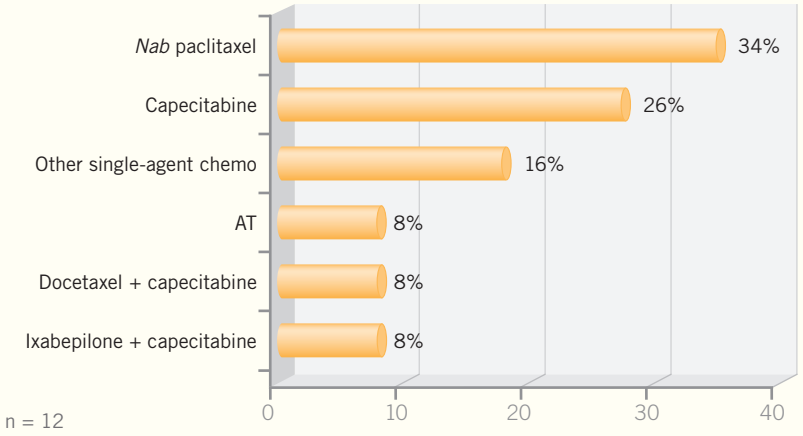
The safety data showed that despite doubling the dose, no increase in side effects occurred. In addition, because the PFS curve is longer, patients were receiving the 500-mg dose longer, and the side-effect profile was essentially the same.

DR SPARANO: In a recent trial, the CONFIRM trial, a higher dose of fulvestrant was used than was used in the EFECT trial, which showed better efficacy and led to the recent approval of the 500-mg dose by the FDA. So I believe fulvestrant is a reasonable choice, especially if the patient develops a recurrence while receiving a steroidal AI such as exemestane.

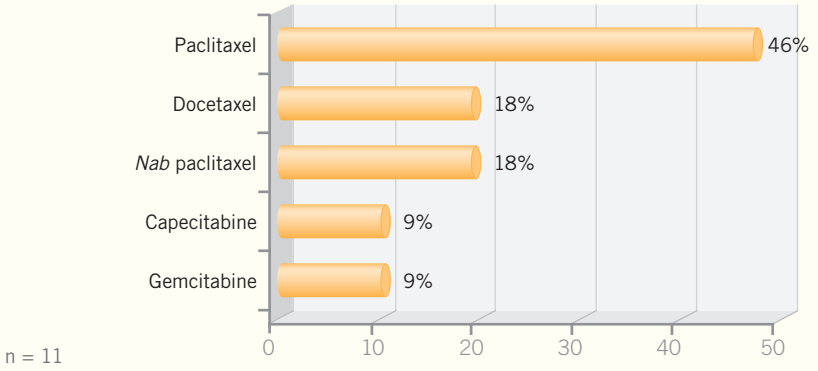
The CONFIRM trial suggests that even for patients who've received prior nonsteroidal AI therapy like anastrozole or letrozole, high-dose fulvestrant may be a better choice. I use that myself.

FIGURE 18

For the patient described in Clinical Scenario 9 (Figure 15), which chemotherapy regimen would you recommend?



If you were to recommend bevacizumab, which chemotherapy would you combine it with?



Breast Cancer Update
Issue 4, 2010

DR MATTHEW ELLIS: I often use capecitabine for patients who've finally gotten to the end of my endocrine cascade, which is pretty prolonged — I'll try endocrine agents until I'm convinced their disease is refractory. Then I'll go to capecitabine. I find the response to capecitabine extremely high in that circumstance.

I would like to find time to research the capecitabine response rate in hormone-refractory ER-positive disease because I'd bet 60 to 80 percent of patients are experiencing clinical benefit. I use the one-week-on/one-week-off schedule, and patients fare well with it.

For the ER-positive, HER2-negative subset, I use a lot of oral chemotherapy. I only go to IV chemotherapy late in the game. For patients with ER-negative, HER2-negative disease, I use chemotherapy. And I do what everyone else does. That's probably the situation in which I've used a lot of bevacizumab — aggressive disease with a lot of visceral crises for which the sort of response acceleration you obtain with bevacizumab is useful.

Breast Cancer Update
Issue 4, 2010

DR CHARLES GEYER: I tend to use the albumin-bound formulation of paclitaxel for patients with metastatic breast cancer, I guess because I'm convinced that it does offer advantages in terms of neuropathy. I believe neuropathy develops later, and I am always bothered when I have to stop the standard paclitaxel formulation earlier than I want to because of neuropathy. The patient isn't receiving as much drug as I would like her to, and she then has this persisting problem that can make subsequent therapies with agents such as ixabepilone more problematic.

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Di Leo A et al. **Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer.** *J Clin Oncol* 2010;28(30):4594-600.

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Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76.

Pritchard KI et al. **Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2).** *Breast Cancer Res Treat* 2010;123(2):453-61.

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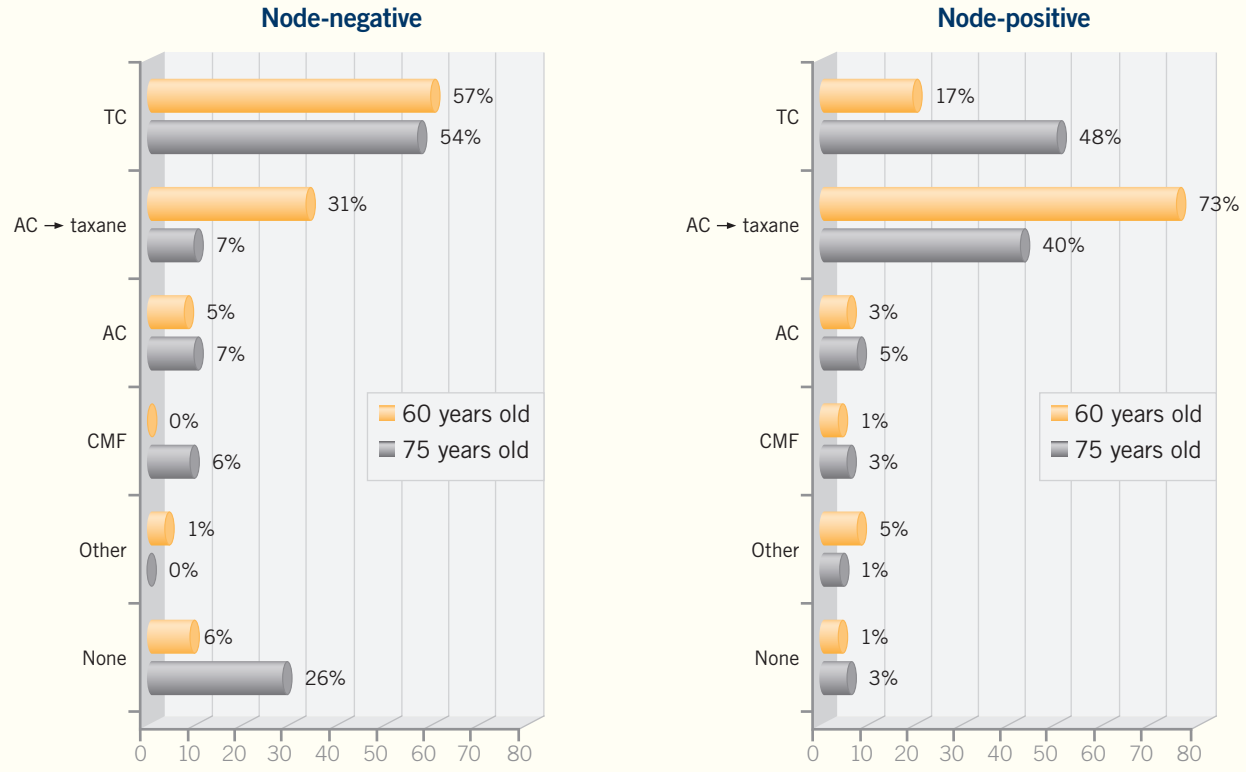
Robertson JFR et al. **Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: Results from the FIRST study.** *J Clin Oncol* 2009;27(27):4530-5.

Warm M et al. **Benefits of early and prolonged fulvestrant treatment in 848 postmenopausal advanced breast cancer patients.** *Breast Cancer Res Treat* 2011;125(1):127-36.

FIGURE 19

Clinical Scenario 10: *A woman has a 1.0-cm, ER/PR/HER2-negative IDC.*

Which of the following adjuvant chemotherapy treatments, if any, would you most likely recommend for this patient if her age and nodal status were:



Adjuvant therapy for triple-negative disease

DR WINER: In this situation with the patient's disease being triple-negative, I believe that we can feel more confident that chemotherapy will be that much more effective. For the 60-year-old patient with a 1-cm, triple-negative tumor, some would opt for an anthracycline/taxane combination. Based on the fairly limited size of the tumor and the negative lymph nodes, many clinicians would be comfortable with a first-generation chemotherapy regimen. It's interesting that we have been seeing movement toward the use of docetaxel/cyclophosphamide.

In triple-negative disease most recurrences occur within five years. I would not have difficulty conceiving of administering a course of chemotherapy to a patient with triple-negative breast cancer who is otherwise healthy and 75 years old. If in fact you prevent recurrence, you almost certainly prevent death, and that is going to be an issue in the next five years — not something that's going to extend out over many, many years.

I don't believe I've administered adjuvant chemotherapy to anyone older than age 80. Even with triple-negative breast cancer, I would have strong reservations about doing that, although I wouldn't absolutely say no.

I would want to make sure that the patient was extremely healthy and I would want to consider the potential effect of chemotherapy on her quality of life and the potential medical complications that could arise. We know that older women do have more serious medical complications with a course of chemotherapy.

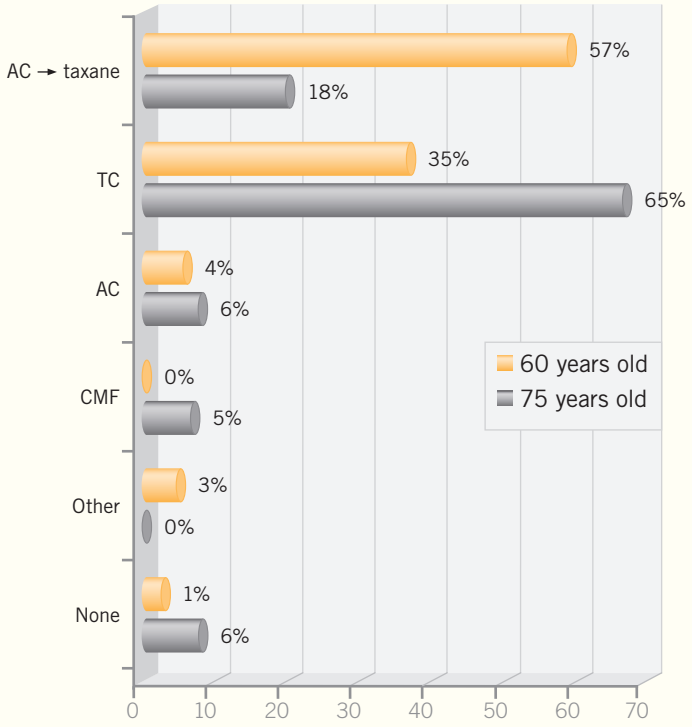
Breast Cancer Update *Issue 1, 2010*

PROF IAN SMITH: I recently conducted a review and no clear-cut chemotherapy for triple-negative breast cancer is better than any other chemotherapy, but some hints and clues emerged. In the original CALGB study of AC/paclitaxel versus AC, Dan Hayes conducted a retrospective analysis to determine which subgroups benefited most from the addition of paclitaxel and identified those with HER2-positive disease or triple-negative breast cancer. So I believe a

FIGURE 20

Clinical Scenario 11: *A woman has a* ***3.4-cm,*** *ER/PR/HER2-negative,* ***node-negative IDC (3 sentinel nodes).***

Which of the following adjuvant chemotherapy treatments, if any, would you most likely recommend in this case if the patient's age was:



taxane should be included in the treatment for triple-negative disease.

Of course, the data for the platinum salts — cisplatin and carboplatin — are extrapolated from the BRCA1 story and experimental data, and many trials are ongoing. We are involved in the ongoing prospective TNT trial comparing carboplatin to standard chemotherapy, and we have retrospectively evaluated our experience in treating triple-negative breast cancer with platinum-based chemotherapy. Our data did not indicate that carboplatin or cisplatin is strikingly superior to other drugs.

Approximately 25 to 30 percent of patients with triple-negative breast cancer have disease that is chemosensitive, and it probably isn't crucial which chemotherapy is used. For the remainder of patients, it's important to move away from chemotherapy and use newer agents.

Breast Cancer Update
Issue 4, 2010

DR MILLER: For a younger patient with a triple-negative breast tumor larger than one centimeter, I would recommend dose-dense AC → T or enrollment in our ECOG study 5103, which is evaluating chemotherapy/bevacizumab. If the patient had a tumor smaller than one centimeter, I'm not certain that I would administer chemotherapy, but it's difficult to be definitive based on size. The decision is partly determined by tumor-related characteristics, the patient's perception of risk and the toxicity she is willing to accept for potential benefit.

In general, I would try not to think about chemotherapy if the tumor is smaller than one centimeter. But if it's high-grade triple-negative breast cancer with a tumor size of eight or nine millimeters and the patient is exceedingly anxious about her risk of recurrence and is not troubled by the acute toxicities of chemotherapy, would I administer chemotherapy? Sure. So I have a hard time trying to put up arbitrary boundaries because many things go into the decisions that would make me willing to behave differently.

We also have a trial specifically for patients with either sporadic triple-negative breast cancer or known BRCA1 or 2 mutation carriers who received neoadjuvant chemotherapy and still have substantial residual disease at the time of surgery. That's a group that has a huge risk of recurrence. This multicenter study will randomly assign patients to four cycles of cisplatin or four cycles of cisplatin with a PARP inhibitor. The PARP inhibitor will then be continued for six months of maintenance therapy.

Breast Cancer Update
Issue 4, 2010

DR C KENT OSBORNE: Clinically, it seems about half of triple-negative breast cancer cases are different from the other half, in the sense that they seem to behave and have a genetic profile similar to cases in which BRCA1 mutations are present. It's not that these patients have BRCA1 mutations, but they could have deficits in the pathway aside from BRCA1. But these tumors' gene profile — if you look at all the genes involved — seems to be similar to those from patients with BRCA1 mutations. Those are the subsets of triple-negative breast cancer that seem to respond to DNA-damaging agents, whereas they don't respond well to drugs like paclitaxel, for example.

Jenny Chang, Angel Rodriguez and our group have been trying to develop a clinically useful BRCA1 signature, and many other groups are trying to do the same thing with different technologies. If we can accomplish that, it'll be a major advance because then we'll be able to identify the specific tumors that are likely to benefit from therapies that

FIGURE 21

BEATRICE: A Phase III study of adjuvant bevacizumab therapy in triple-negative breast cancer

Protocol ID: BO20289

Target Accrual: 2,530

Eligibility

Operable triple-negative breast cancer without clinically significant cardiac history

R

- Standard chemotherapy*
- Standard chemotherapy* + bevacizumab x 1 y

Primary Endpoint: Invasive disease-free survival

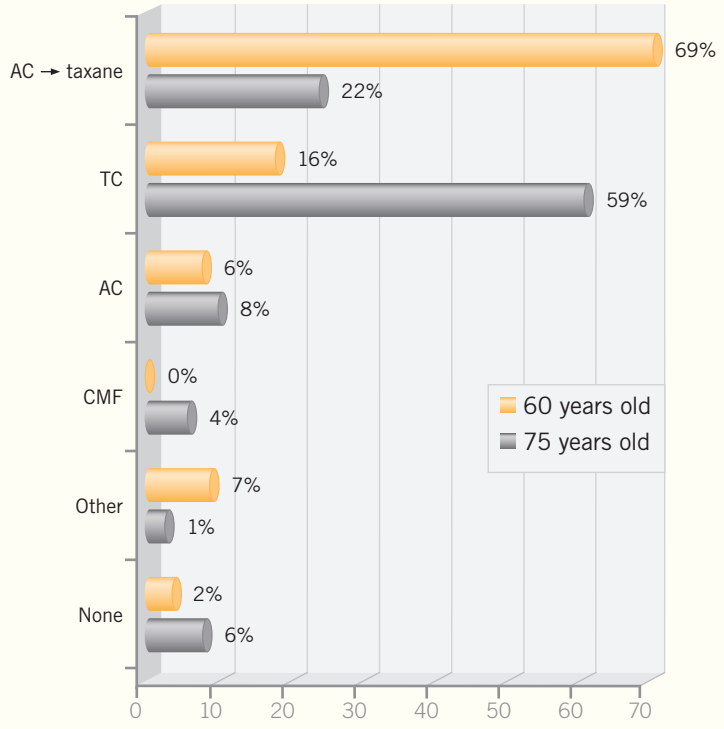
* Anthracycline ± taxane or taxane only

www.clinicaltrials.gov. Accessed March 2011.

FIGURE 22

Clinical Scenario 12: *A woman has a core biopsy as follows: 4-cm, ER/PR/HER2-negative, node-negative IDC (3 sentinel nodes). The patient wishes to undergo breast-conserving surgery, which will be difficult or impossible without shrinkage of the breast mass, so* ***neoadjuvant therapy*** *is being considered.*

Which of the following chemotherapy treatments, if any, would you most likely recommend in this case if the patient's age was:



block DNA repair and are likely to have a good response.

It's also likely that patients with other kinds of breast cancer besides triple-negative tumors will have this deficiency and may benefit from drugs like PARP inhibitors. So we need a way of selecting those patients, and one of the ways is with a DNA signature or an RNA expression signature. Alan Ashworth's group in London is trying to come up with other, more functional assays to select these patients.

Neoadjuvant therapy

Breast Cancer Update *Issue 1, 2011*

PROF MICHAEL UNTCH: In the GEPAR-QUINTO neoadjuvant study of patients with HER2-negative breast cancer, only one subgroup of patients seems to benefit from the combination of chemotherapy with bevacizumab, which is the patient subset with triple-negative disease. So I am curious to see what our American colleagues are going to find out in the NSABP-B-40 study evaluating adjuvant bevacizumab and, of course, also the subgroup analysis of the triple-negatives.

Maybe we'll learn a lesson from the neoadjuvant studies that will apply to the adjuvant setting. I would bet that the ongoing US study for patients with triple-negative breast cancer will show a benefit for adjuvant bevacizumab in this breast cancer subtype (Figure 21).

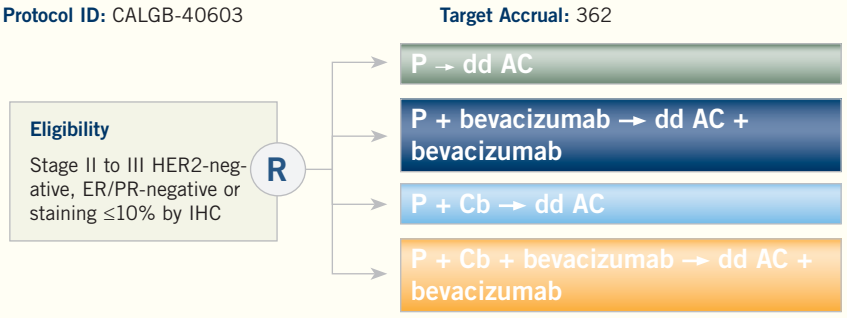
Breast Cancer Update *for Surgeons Issue 2, 2009*

DR LISA CAREY: ECOG-E2100 is the pivotal trial that examined the effect of adding bevacizumab to paclitaxel in the metastatic setting, and it demonstrated that if you add an anti-angiogenic agent to chemotherapy for metastatic disease, patients fare better. They have a longer PFS.

In the subset of patients who had largely triple-negative disease, a similar benefit or maybe even a slightly greater benefit was seen in comparison to the average patient in the trial. So that suggests that we may have a targeted agent

FIGURE 23

Randomized Phase II 2 x 2 factorial trial of the addition of carboplatin with or without bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC in hormone receptor-poor/HER2-negative resectable breast cancer



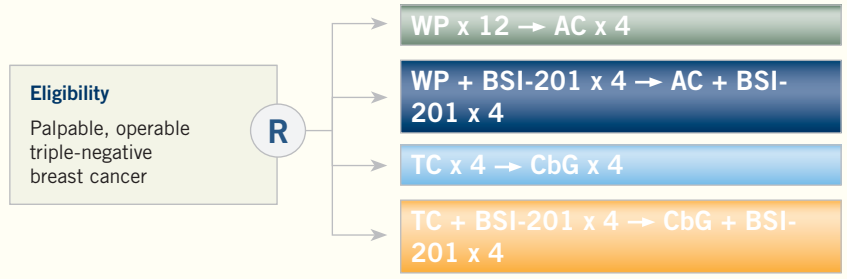
Primary Endpoint: Pathologic complete response

P = paclitaxel
dd AC = dose-dense doxorubicin/cyclophosphamide
Cb = carboplatin

www.clinicaltrials.gov. Accessed March 2011.

FIGURE 24

Randomized Phase III neoadjuvant trial in triple-negative breast cancer evaluating nonanthracycline-containing chemotherapy and PARP inhibition with BSI-201 (iniparib)



Primary Endpoint: Pathologic complete response

WP = weekly paclitaxel 80 mg/m^2 IV
AC = doxorubicin 60 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV
TC = docetaxel 75 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV
CbG = carboplatin AUC of 2.0 IV + gemcitabine 1,000 mg/m^2 IV

NSABP Protocol Summaries, April 2010.

with anti-angiogenic strategies in triple-negative disease that would be effective.

That is being tested directly in the ongoing CALGB-40603 neoadjuvant study for triple-negative, clinical Stage II and Stage III breast cancer (Figure 23). Patients are randomly assigned to a taxane with or without bevacizumab that is then followed by dose-dense AC prior to surgery. A secondary randomization to a platinum agent or no platinum agent will also take place.

Breast Cancer Update
Issue 4, 2010

DR GEYER: NSABP-B-48 is a two-by-two design that will target 540 women with triple-negative breast cancer (Figure 24). The primary tumor must be two centimeters or larger, unless patients have palpable axillary nodes that are biopsy-proven to be involved with metastatic cancer. Strictly speaking, patients with ER/PR-negative or weakly ER/PR-positive disease can enroll, and we're lining our eligibility criteria up to match the new ASCO/CAP guidelines. Basically, less than 10 percent of cells positive by IHC will be viewed as weakly positive, so those patients will be included. Importantly, those patients are being included in the Phase III metastatic trial with iniparib, so we wanted to have consistency.

We're using a standard control regimen of weekly paclitaxel times twelve followed by AC for four cycles and comparing that to a nonanthracycline regimen of docetaxel/cyclophosphamide times four followed by the carboplatin/gemcitabine combination that Joyce O'Shaughnessy and her colleagues used in their Phase II study, and it's being carried forward in the Phase III trial. Each chemotherapy option is with or without iniparib.

SELECT PUBLICATIONS

Chang HR et al. **Differential response of triple-negative breast cancer to a docetaxel and carboplatin-based neoadjuvant treatment.** *Cancer* 2010;116(18):4227-37.

Cleator S et al. **Triple-negative breast cancer: Therapeutic options.** *Lancet Oncol* 2007;8(3):235-44.

Colleoni M et al. **Classical cyclophosphamide, methotrexate, and fluorouracil chemotherapy is more effective in triple-negative, node-negative breast cancer: Results from two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer.** *J Clin Oncol* 2010;28(18):2966-73.

Foulkes WD et al. **Triple-negative breast cancer.** *N Engl J Med* 2010;363(20):1938-48.

Perez EA et al. **Adjuvant therapy of triple negative breast cancer.** *Breast Cancer Res Treat* 2010;120(2):285-91.

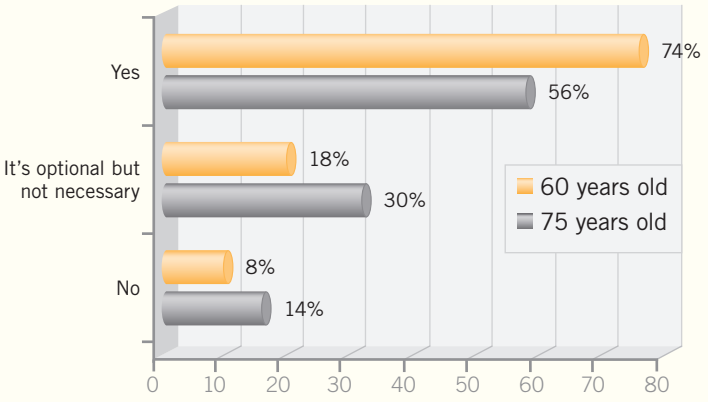
Silver DP et al. **Efficacy of neoadjuvant cisplatin in triple-negative breast cancer.** *J Clin Oncol* 2010;28(7):1145-53.

Von Minckwitz G et al. **Neoadjuvant chemotherapy with or without bevacizumab: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44).** San Antonio Breast Cancer Symposium 2010;**Abstract S4-6**.

FIGURE 25

Clinical Scenario 13: *A postmenopausal woman received dose-dense AC → T 2 years ago for a 2.1-cm, ER/PR/HER2-negative IDC with 3 positive nodes. She now presents with pulmonary nodules and multiple hot spots on bone scan.* ***She is asymptomatic.***

Would you generally obtain a biopsy on one of the metastases in this case if the patient's age was:



Biopsy for asymptomatic metastatic TNBC

DR SPARANO: My own bias would be to perform a biopsy whenever feasible for a variety of reasons. My number one reason would be to confirm that you're dealing with a recurrence of breast cancer and that you're dealing with metastatic breast cancer. I've had scenarios in which biopsies have come back showing sarcoidosis, lymphoma or other cancer types. So establishing the correct diagnosis is critical.

Second, it's known that the tumor can change phenotypes. Breast cancer is known to be heterogeneous. Also, subclones of the tumor may be recurring. It's important to know the biology of recurrent disease.

However, having said that, in some scenarios it may not be possible to perform a biopsy and an overwhelming amount of evidence may suggest that one is dealing with breast cancer — for example, on the basis of a very high tumor marker with extensive bone disease, in which no single bone lesion would be easily accessible for a biopsy.

If this scenario occurs in an older patient or someone with multiple comorbidities, I'd be less inclined to push the biopsy. But I do attempt to do that whenever possible.

DR WINER: I don't understand why age plays a role here because this is about optimizing therapy for metastatic disease, and it's something that's going to affect a woman who's 60 in the same way that it's going to affect a woman who's 75.

I believe the overwhelming likelihood is that this woman will have biopsy-proven triple-negative breast cancer. A little bit of discordance exists in terms of both HER2 and ER. I believe discordance could exist with either of these, but I might be most concerned about making sure that it's a HER2-negative tumor because being able to use anti-HER2 therapy in this kind of situation would make a big difference for her, although the number of cases in which discordance occurs is probably no more than approximately 10 percent.

Endocrine therapy still is a good option, and you'd hate to miss that opportunity. My sense is that if, in fact, this turns out to be ER-positive, it's going to be very low ER-positive. I believe you could also approach it by restaining the original tumor for ER to make sure that no problems occurred then. I believe that you're unlikely to get a surprise, but I would do it, and I would want it restained for ER, PR and HER2.

With this kind of situation, in which somebody had what's said to have been a triple-negative tumor with multiple positive lymph nodes and was at high risk for recurrent disease, I believe the overwhelming majority of the time this is going to be metastatic breast cancer. It would be a different situation if what she presented with a few years ago was a 1-cm, low-grade, ER-positive breast tumor. Then your pretest probability that this is metastatic breast cancer is much, much lower.

Systemic therapy for asymptomatic and symptomatic metastatic TNBC

DR WINER: We know from the studies that have been done that bevacizumab works as well in triple-negative disease as in ER-positive disease. My decision to use bevacizumab is not dissimilar from my decision to use combination versus single-agent chemotherapy, in the sense that if I want to maximize the chance of obtaining a response and if I want to try to maximize the time to disease progression, recognizing that the effect on survival, if any, will be minimal, then I would add bevacizumab.

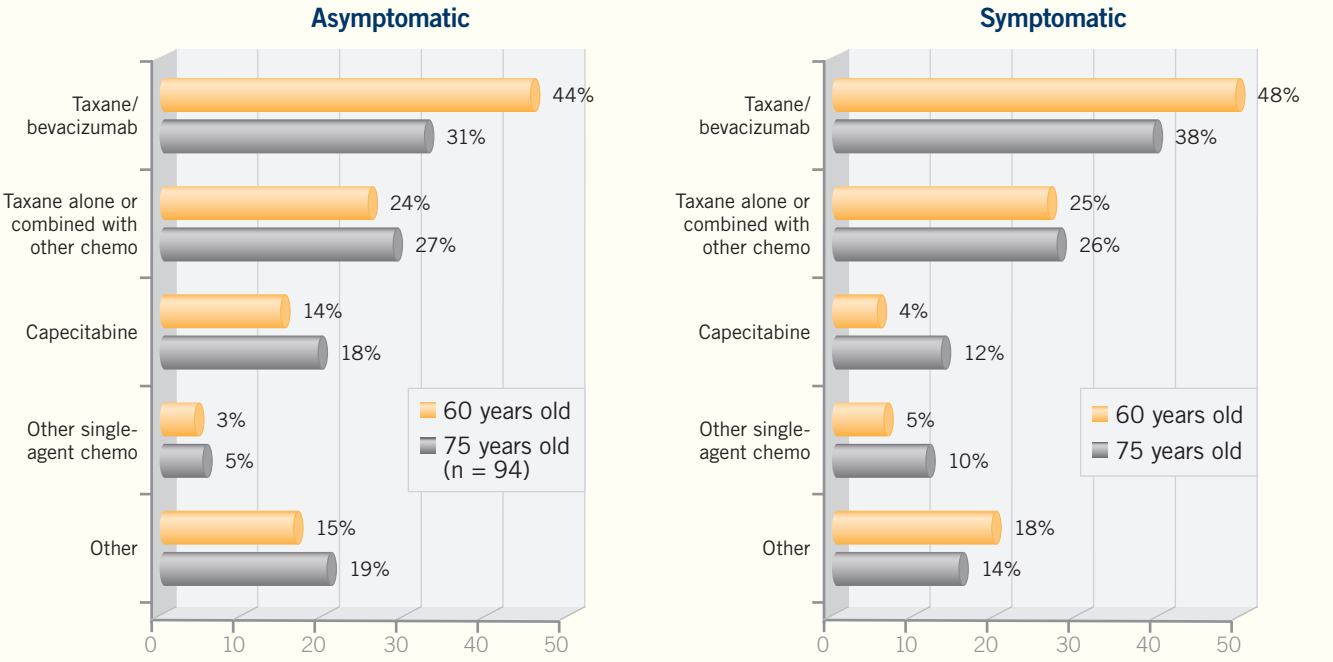
I believe it's rational to do it a little less commonly for a 75-year-old than for a 60-year-old because of the complications. You have to worry more about complications with bevacizumab in older women than in somewhat younger women.

I also believe that the biggest challenge here is that the median survival for women with triple-negative metastatic breast cancer is approximately one year or just a bit more than that. So we

FIGURE 26

Clinical Scenario 14: *A postmenopausal woman received dose-dense AC → T 2 years ago for a 2.1-cm, ER/PR/HER2-negative IDC with 3 positive nodes. She now presents with pulmonary nodules and multiple hot spots on bone scan. Lung biopsy is consistent with the primary tumor.*

Which of the following systemic treatments, if any, would you most likely recommend in this case if the patient's age was:



need new and better therapies. If the patient were asymptomatic and you wanted to minimize toxicity, I wouldn't have any trouble with a trial of capecitabine up front. Outside of a trial, I would use either capecitabine or a taxane with or without bevacizumab. And whatever I did first, I would choose the other second.

I realize that the data have been mixed in terms of using bevacizumab based on age. In the initial ECOG trial, more vascular complications were seen in older women than in younger women. And I believe that it's a concern that one can have. Whether we can say absolutely that a lot more complications occur in older women than in younger women, we're probably not quite there given the mixed data. But I still believe it's more of a concern.

Breast Cancer Update
Think Tank, January 2011

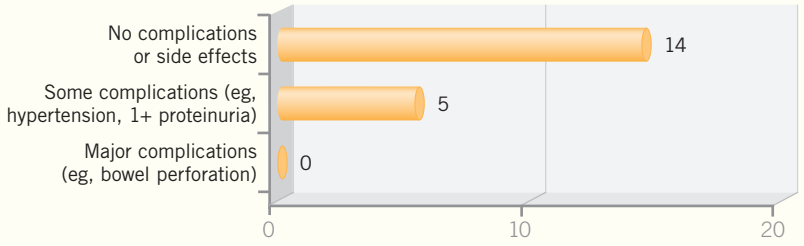
DR GEYER: For the population of patients with triple-negative disease, bevacizumab has an important apparent utility that may not be quite as evident in the ER-positive setting because we have fewer options for the population with triple-negative disease. Things happen more quickly so you work through your toolbox more quickly. Therefore, even if no clear evidence supports a greater activity level in triple-negative disease relative to ER-positive disease, when trying to provide palliation to a woman with triple-negative breast cancer, the bevacizumab contribution may have greater absolute value for that patient than it would for a patient with HER2-positive or ER-positive disease simply because the treatment options are so much more limited.

Bevacizumab-associated clinical benefits and risks

DR SPARANO: I believe that bevacizumab does have a clinically useful role in the management of metastatic breast cancer but only when used in specific situations. Many have focused on the lack of a survival benefit when one considers the aggregate data sets. And this has focused on a lack of benefit for median survival. What's been lost in the whole discussion is the fact that a consistent benefit occurs that's clinically significant for survival at one year. In each of the individual studies and in the meta-analysis, an approximately five percent absolute improvement in survival at one year is seen, inclusive of the subset with triple-negative disease (Figure 28). This is during a period when the patient is receiving the drug, with the average treatment duration being about nine to 12 months.

FIGURE 27

Approximately how many of your patients who have received treatment with bevacizumab experienced...



Median values reported: n = 99

Which of the following best describes your perspective on the potential clinical benefit-risk ratio of bevacizumab (in combination with chemotherapy) in metastatic breast cancer?

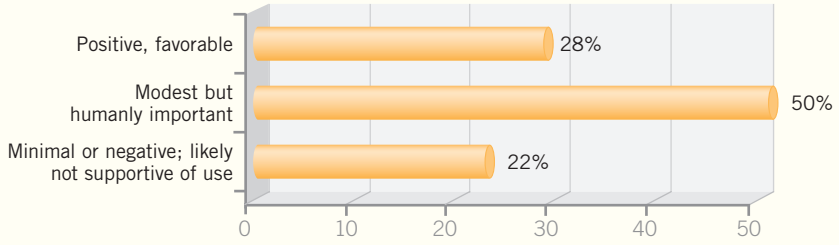


FIGURE 28

Meta-analysis of patients with triple-negative disease from 3 randomized trials of bevacizumab and first-line chemotherapy as treatment for metastatic breast cancer (n = 621)

Outcome	Bevacizumab + chemotherapy (n = 363)	Chemotherapy alone (n = 258)	Hazard ratio*	*p*-value
Objective response	42%	23%	—	<0.0001
Progression-free survival (PFS), events	71%	75%	0.649	<0.0001
Median PFS	8.1 months	5.4 months	—	—
Overall survival (OS), events	68%	67%	0.959	0.6732
Median OS	18.9 months	17.5 months	—	—
One-year OS rate	70.9%	64.8%	—	0.1140

* Unstratified analysis

O'Shaughnessy J et al. San Antonio Breast Cancer Symposium 2010; **Abstract P6-12-03**.

So I believe that tells me two things. Number one, the drug is safe. I know some concerns have been raised that adding bevacizumab may increase life-threatening or lethal toxicities associated with therapy. But survival at one year, at a point in time that reflects when the patient's receiving the drug, I believe reflects the safety of the drug.

Second, I believe it also reflects the efficacy of the drug. We may not be using the drug properly. One may see rebound angiogenesis when one discontinues the drug, and one may actually need to continue the drug beyond disease progression, as was the case with trastuzumab. For many years we suspected that might be the case, and many patients continued trastuzumab beyond disease progression. We have not done that with bevacizumab and, unfortunately, the proper trial has not been designed to address that question.

DR WINER: I wish I knew the patients who seem to obtain the greatest benefit from bevacizumab. My impression — and this would be consistent with the trials — is that a subset of patients obtain a clear benefit from bevacizumab. I don't believe it's every single patient. But we still struggle to know how to identify those patients.

In the ideal world, I would like to see bevacizumab remain as an option. I don't believe it is the standard. I believe it is a reasonable treatment to consider. But I don't believe we have a single standard at this moment for the treatment of first-line metastatic breast cancer. So the bottom line is I would like to have it continue to be available as an option and I would use it in situations in which I felt that a patient needed the best disease control as soon as possible.

Capecitabine/ixabepilone for TNBC

Breast Cancer Update
Issue 3, 2010

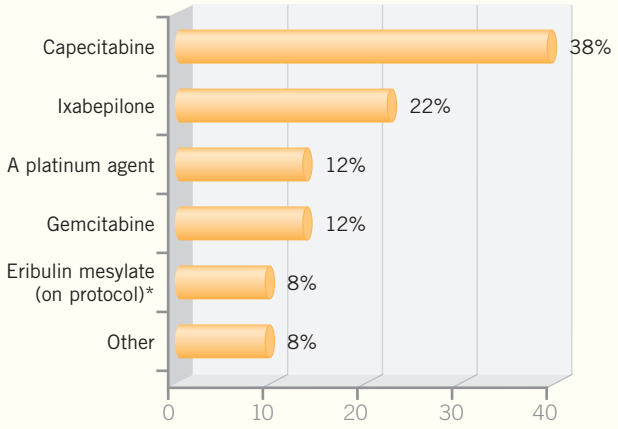
DR LINDA VAHDAT: The combination of ixabepilone and capecitabine is supported by data in triple-negative disease, as seen in the pooled analysis of two large Phase III trials evaluating capecitabine with or

FIGURE 29

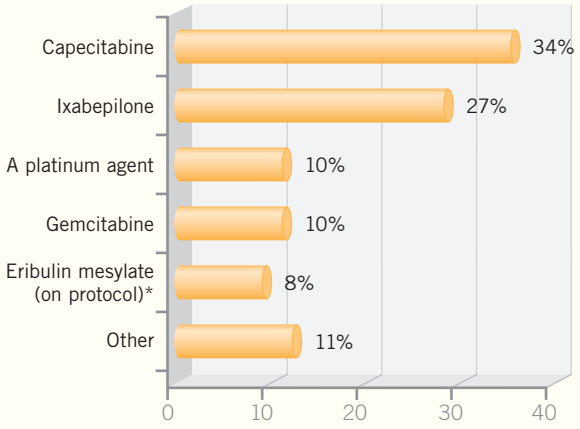
A postmenopausal woman received dose-dense AC → T 2 years ago for a 2.1-cm, ER/PR/HER2-negative IDC with 3 positive nodes. She then presents with pulmonary nodules and multiple hot spots on bone scan causing diffuse bone pain and some dyspnea and receives nanoparticle albumin-bound (nab) paclitaxel and bevacizumab off protocol. She now has progressive disease in her liver and bone.

Which chemotherapy, if any, would you most likely recommend for the patient at this time if the patient experienced...

Partial tumor response, pain control for 9 months



Stable disease for 4 months



* This use of eribulin mesylate had not been approved by the FDA at the time of this survey in October 2010.

Would you continue the bevacizumab with this chemotherapy?

FIGURE 30

Pooled analysis of 2 Phase III trials evaluating ixabepilone (ixa) with or without capecitabine for patients with triple-negative metastatic breast cancer

	Capecitabine	Capecitabine + ixa	Hazard ratio	*p*-value
Overall response rate (n = 208, 191)	15%	31%	—	—
Median progression-free survival (n = 208, 191)	1.7 mo	4.2 mo	0.63	<0.0001
Median overall survival (n = 230, 213)	9.0 mo	10.3 mo	0.87	0.1802

Rugo HS et al. San Antonio Breast Cancer Symposium 2008;**Abstract 3057**.

without ixabepilone (Figure 30). This pooled analysis also showed that for patients experiencing disease progression within one year of completing adjuvant therapy, the response rate with the combination was high.

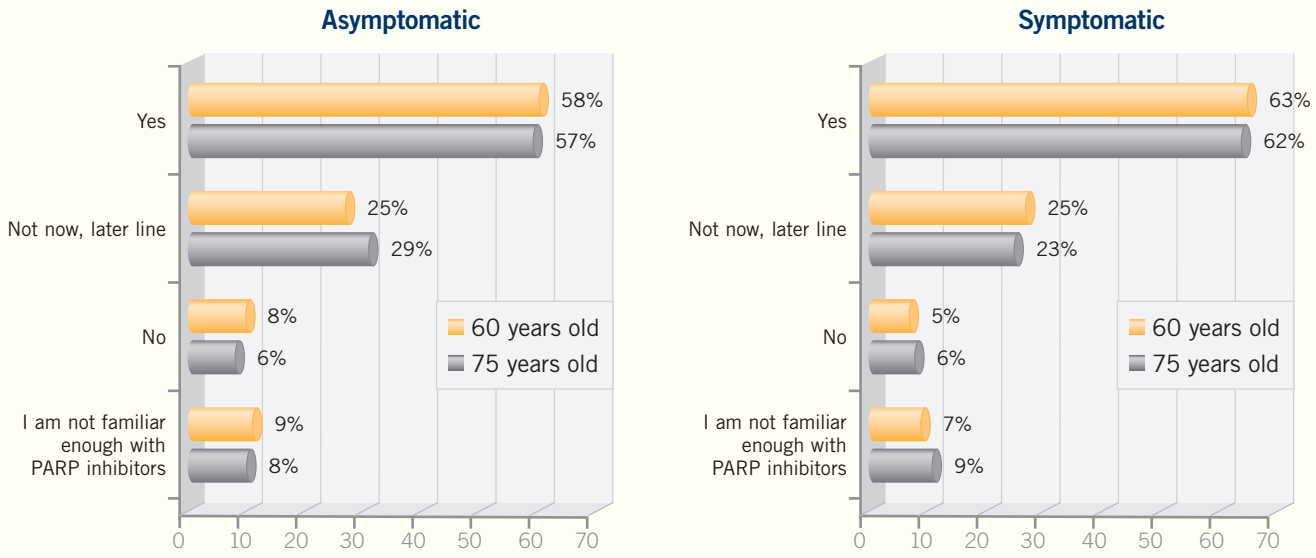
Breast Cancer Update
Think Tank Issue 1, 2010

DR EDITH PEREZ: The data with ixabepilone for triple-negative breast cancer are strongly suggestive of benefit. I believe the best study to have evaluated this in a pure fashion is a neoadjuvant study published by José Baselga and colleagues in the *JCO* evaluating ixabepilone at 40 mg/m^2 for four doses in a large number of patients in the neoadjuvant setting. Overall, the pCR rate was about 18 percent for ixabepilone alone. In the subgroup of patients with

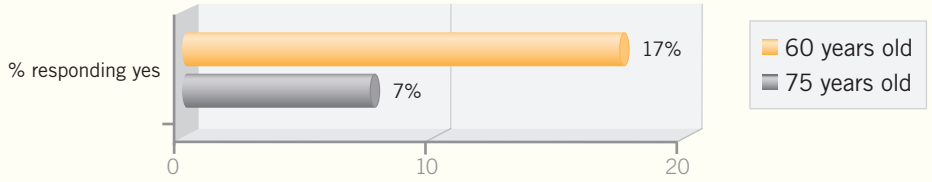
FIGURE 31

A postmenopausal woman received dose-dense AC → T 2 years ago for a 2.1-cm, ER/PR/HER2-negative IDC with 3 positive nodes. She now presents with pulmonary nodules and multiple hot spots on bone scan.

If a PARP inhibitor were available for this patient, either on or off study, would you recommend it for the patient?



The patient's family history is negative for breast and ovarian cancer. Would you test this patient for BRCA mutations?



triple-negative disease, the pCR rate was 26 percent. So these are provocative data that are worthy of consideration by clinicians and in further studies.

PARP inhibitors for TNBC

DR SPARANO: Unfortunately, PARP inhibitors are largely unavailable, except through clinical trials or through a compassionate-use program for iniparib. We're anxiously awaiting the full results of the confirmatory trial. We expect them sometime in 2011. That trial was nearly identical in design to the original trial presented by Joyce O'Shaughnessy and, if positive, will undoubtedly lead to approval of iniparib to be used in combination with carboplatin and gemcitabine.

Until that time, it's clear that this class of drugs has activity, but many unknowns still exist. Do these drugs have comparable activity, and are they interchangeable? What are the biomarkers that predict benefit from these agents? Do they have similar effects irrespective of what chemotherapy agent or agents you partner them with, or do their benefits occur only when administered with specific chemotherapy regimens? I believe in the next couple of years we'll begin to see some answers to these important questions.

The original Phase II trial included patients who had received zero to two prior chemotherapy regimens. The trial wasn't sufficiently powered to identify the benefit in patients who had received less extensive treatment versus more extensive treatment. And we don't know information in that regard concerning the confirmatory Phase III trial. So I believe we're going to need more information before we can figure out exactly how to use this drug — whether it would be better used as a component of first-line therapy or whether it might be best to reserve it after several lines of therapy have failed in patients.

DR WINER: I would like to use iniparib in the first-line setting because if what was seen in Phase II is seen in Phase III,

FIGURE 32

Final efficacy results of the Phase II trial of iniparib (BSI-201) in combination with gemcitabine/carboplatin (gem/carbo) for patients with metastatic triple-negative breast cancer

Clinical variable	Gem/carbo (n = 62)	Iniparib/gem/carbo (n = 61)	*p*-value*
ORR	32%	52%	0.02
CBR	34%	56%	0.01
Median PFS	3.6 mo	5.9 mo	0.01
Median OS	7.7 mo	12.3 mo	0.01

* Not adjusted for multiple interim analyses
ORR = objective response rate; CBR = clinical benefit rate; PFS = progression-free survival; OS = overall survival

O'Shaughnessy J et al. *N Engl J Med* 2011;364(3):205-14.

then it's a drug that leads to a survival benefit (Figure 32). I don't necessarily love the carboplatin/gemcitabine combination, but it's the regimen that's been combined with iniparib and if, in fact, a survival benefit with carboplatin/gemcitabine in combination with iniparib versus carboplatin/gemcitabine occurs, then I would tend to use that regimen outside of a trial in the first line. I don't believe that means that the trials end. I believe we need to sort out how best to use the PARP inhibitors and with what agents. Do you need both gemcitabine and carboplatin? I believe a whole range of questions persist.

DR SPARANO: With regard to iniparib, or BSI-201, one of the striking findings from the O'Shaughnessy study was that the addition of iniparib did not seem to add any substantial toxicity associated with the carboplatin/gemcitabine regimen. The major issue was probably the inconvenience of requiring the twice-weekly schedule of drug administration during the first two weeks.

Testing for BRCA gene mutations

DR SPARANO: If patients meet the established NCCN guidelines for BRCA testing, it should be considered. I believe in the past we've only thought of testing as a means to potentially counsel the patients and their family members, but now I believe we may need to think of testing because it may have therapeutic implications for the patient who has metastatic breast cancer, whether it is triple-negative or ER-positive, because PARP inhibitors as single agents can be effective if patients are known to be BRCA mutation-positive.

So for the patients who have recurrent disease and who may not have been tested, I believe we're going to have additional reasons to consider testing them — so that we can identify those who may harbor mutations and, therefore, may be exquisitely sensitive to these agents, either used alone or in combination with other agents.

I generally refer all of my patients with TNBC to a genetic counselor at my institution. So I haven't run into a situation in which I've ordered the test for someone who hasn't previously been BRCA tested solely to identify whether they, for example, may be a candidate for a PARP inhibitor. But I believe that scenario will become more common in the near future.

DR WINER: Triple-negative tumors are more commonly seen in association with BRCA1 — not BRCA2 — mutations. If we get to the point that we have an agent available commercially and we know it specifically works for patients with BRCA1 or BRCA1 and 2 mutations, then I believe we'll see more of a push to perform genetic testing. So, for example, olaparib, the PARP inhibitor that's been evaluated in ovarian cancer and breast cancer as a single agent, appears to work specifically in patients who have mutations. If that drug becomes available, then I believe that the threshold to test is going to go down.

To the best of my knowledge, BSI-201, or iniparib, is not a drug that requires the presence of a BRCA1 or BRCA2 mutation to augment the effectiveness of chemotherapy. And any approval would be for, I presume, triple-negative breast cancer. So I don't believe that's a reason to do testing.

You might argue for a patient with triple-negative breast cancer in the metastatic setting to try a platinum salt at some point along the way. And I don't know that a mutation is going to push me that much more in the direction of using a platinum salt. You could do it.

I'm aware of a preoperative trial from Poland, in which four cycles of single-agent cisplatin were associated with a remarkably high pCR rate in women with triple-negative, BRCA1-associated cancer. But beyond that trial and beyond a lot of preclinical evidence, I'm not sure that we know that the platinum salts are better than other drugs. And even in that trial we don't know that they're better than other chemotherapy agents for patients with metastatic triple-negative disease.

SELECT PUBLICATIONS

Baselga J et al. **Cetuximab + cisplatin in estrogen receptor-negative, progesterone receptor-negative, HER2-negative (triple-negative) metastatic breast cancer: Results of the randomized Phase II BALI-1 trial.** San Antonio Breast Cancer Symposium 2010;**Abstract PD01-01**.

Kassam F et al. **Survival outcomes for patients with metastatic triple-negative breast cancer: Implications for clinical practice and trial design.** *Clin Breast Cancer* 2009;9(1):29-33.

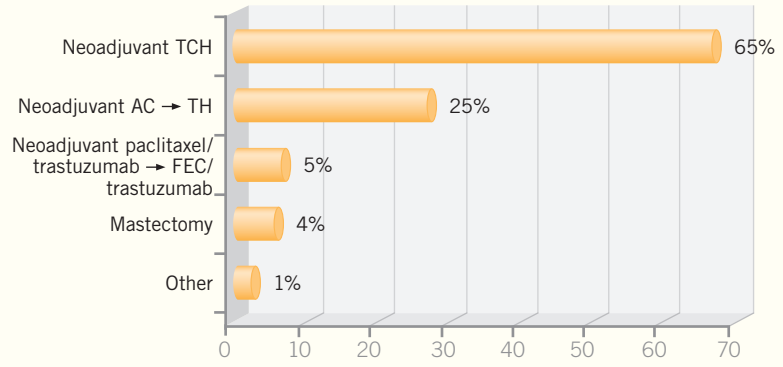
O'Shaughnessy J et al. **Iniparib plus chemotherapy in metastatic triple-negative breast cancer.** *N Engl J Med* 2011;364(3):205-14.

O'Shaughnessy J et al. **Meta-analysis of patients with triple-negative breast cancer (TNBC) from three randomized trials of first-line bevacizumab (BV) and chemotherapy treatment for metastatic breast cancer (MBC).** San Antonio Breast Cancer Symposium 2010;**Abstract P6-12-03**.

FIGURE 33

*A 60-year-old woman has a core biopsy as follows: 4.8-cm, ER-positive, **HER2-positive**, node-positive IDC **(3 sentinel nodes)**. The patient wishes to undergo **breast-conserving surgery,** which will be difficult or impossible without shrinkage of the breast mass.*

Which of the following would be your most likely recommendation for this patient?



Neoadjuvant treatment selection for HER2-positive BC

DR WINER: I am not sure it makes a difference which chemotherapy is combined with trastuzumab in the neoadjuvant setting. The question will be whether adding lapatinib or adding pertuzumab substantially increases the pCR rate. But even if it does, it's still going to take longer-term follow-up to drive clinical behavior, at least in my view.

The NeoALTTO study evaluates paclitaxel/trastuzumab versus paclitaxel/lapatinib versus paclitaxel and the combination, but again, it only evaluates pCR as the outcome measure.

The NeoSPHERE study evaluates docetaxel/trastuzumab, docetaxel/pertuzumab or docetaxel/combination versus the biologic agents alone. The German study simply compares chemotherapy in combination with trastuzumab to chemotherapy in combination with lapatinib.

I believe all of it will be interesting. If the NeoALTTO study suggests that the combination arm is better, then it's going to be interesting to see what the ALTTO trial shows. But the real question is when an improvement in pCR occurs, is that improvement a result of patients who would have fared well anyway? Or is it because of the ability to salvage patients who wouldn't have fared well?

We enroll most of these patients on the CALGB trial that is evaluating paclitaxel/trastuzumab versus paclitaxel/lapatinib versus paclitaxel in combination with the two biologic agents together. And outside of a trial, we typically administer paclitaxel and trastuzumab as the initial regimen and then follow that with an anthracycline, typically after surgery.

It's just reversing the regimen. It's been done before in George Sledge's old ECOG pilot before the randomized adjuvant trials. I believe that is how they administered AC and TH. They administered TH followed by AC.

Breast Cancer Update
Issue 1, 2011

PROF UNTCH: The HER2-positive component of the GEPARQUINTO study evaluated 620 patients with HER2-positive early breast cancer, left ventricular ejection fractions of 55 percent or more and tumors two centimeters or larger by palpation or one centimeter or larger by ultrasound — though the average tumor size on the trial was four centimeters.

Patients were randomly assigned to 24 weeks of epirubicin/cyclophosphamide followed by four cycles of docetaxel with either trastuzumab or lapatinib.

This was the first clinical trial to compare chemotherapy/trastuzumab to chemotherapy/lapatinib. According to NSABP criteria, the pCR rate was 50 percent with chemotherapy/trastuzumab and 35 percent with chemotherapy/lapatinib, which was unexpectedly lower than what was hypothesized at the beginning of this study.

In the intent-to-treat analysis, 23 percent of patients on the chemotherapy/lapatinib arm had treatment discontinued compared to a 13 percent rate of discontinuation in patients who received chemotherapy/trastuzumab.

This was the first time that lapatinib has been administered with anthracyclines and docetaxel, and we had to learn how to cope with the side effects of this combination. We learned that it was necessary to reduce the daily dose of lapatinib from 1,250 mg to 1,000 mg to avoid diarrhea, and we also learned to add G-CSF to avoid febrile neutropenia from lapatinib and docetaxel. These are important lessons learned from this trial, and we now discuss with patients which side effects to expect and how to deal with them.

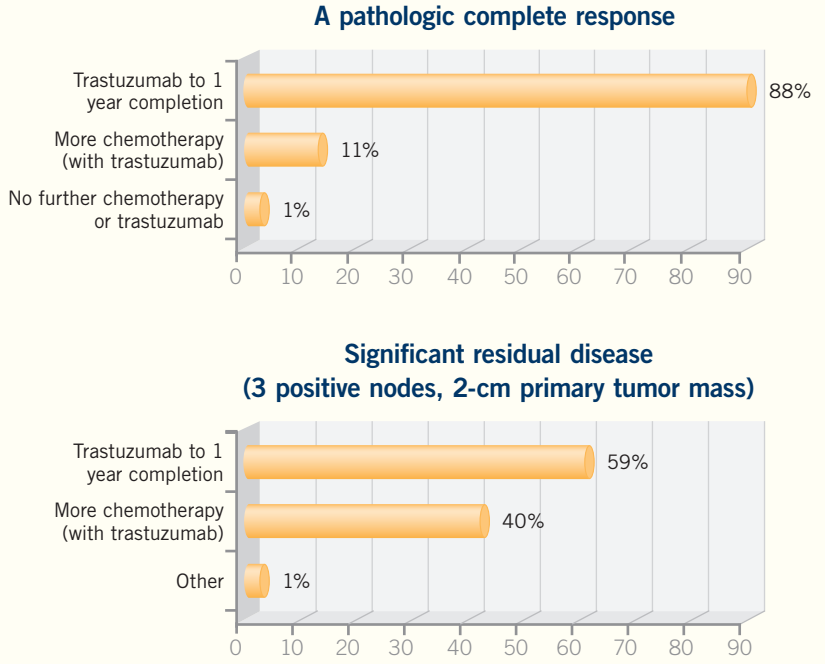
The concept of dual receptor targeting with lapatinib and trastuzumab is that they attack the tumor cell from the outside with trastuzumab and from the inside with lapatinib. This principle was shown in the NeoALTTO trial, in which the authors reported an extremely nice synergistic effect with the combination of trastuzumab and lapatinib.

I wonder whether this will also be the case with the more than 8,000-patient

FIGURE 34

*A 60-year-old woman has a core biopsy as follows: 4.8-cm, ER-positive, **HER2-positive**, node-positive IDC **(3 sentinel nodes)**. The patient wishes to undergo **breast-conserving surgery**, which will be difficult or impossible without shrinkage of the breast mass. **She receives TCH (docetaxel/carboplatin/trastuzumab) for 6 cycles**.*

*In addition to endocrine therapy, which of the following would you most likely recommend as **systemic** postop treatment if this patient had...*



ALTTO study in the adjuvant setting. I would await additional results with dual receptor combination inhibitors before using the approach outside of a protocol setting.

Breast Cancer Update
Issue 1, 2011

DR LUCA GIANNI: The design of the NeoSPHERE trial was simple. We decided to evaluate the use of neoadjuvant drugs and to rank the efficacy of the treatments we tested. We used conventional treatment, consisting of trastuzumab with docetaxel, as a comparator, and we also studied a triple combination of pertuzumab/trastuzumab/docetaxel.

Because the laboratory and clinical data associated with pertuzumab/trastuzumab were favorable, we designed an arm on which women received only the two monoclonal antibodies for four cycles.

We found that the triple combination of docetaxel/trastuzumab/pertuzumab was associated with a high rate — 45.8 percent — of pCR in the breast, which was significantly higher than that of the conventional treatment with docetaxel and trastuzumab — 29 percent.

Adjuvant therapy for elderly patients with HER2-positive BC

Breast Cancer Update
Issue 4, 2008

DR HYMAN MUSS: It would be great to have a clinical trial of trastuzumab versus no trastuzumab, especially for older patients, although I believe it would be hard to complete conceptually because if patients were healthy, they would receive chemotherapy and trastuzumab. You'd be left with patients who were sicker and more frail, and then you'd have to randomly assign them. They'd have smaller tumors and lower event rates. Once we sat down and evaluated what kind of sample size we needed, such a trial would be difficult to conduct.

I have not used trastuzumab without chemotherapy. A trial run by Dana-Farber, in which we're participating, is evaluating weekly paclitaxel and trastuzumab in the adjuvant setting. We know that paclitaxel/trastuzumab is an effective combination in the metastatic setting.

Weekly paclitaxel has been a reasonably well-tolerated chemotherapy, irrespective of age. I believe it's a good design. It's a modest amount of chemotherapy — 12 cycles of weekly paclitaxel. Should you use that outside of a clinical trial? I would administer something like TC with trastuzumab as in the HERA trial if the patient were healthy enough.

DR SPARANO: Paclitaxel and trastuzumab is one of the treatment choices selected for older patients, and it can be administered in several ways. One would be weekly paclitaxel with trastuzumab. In that case, the rate of Grade 2 to 4 neuropathy would be approximately 20 to 25 percent. So that would be a potential downside. That rate of neuropathy is probably higher than with the other regimens described. However, nonhematologic and hematologic toxicities would be more favorable.

Another way to administer the single agent would be to administer four cycles of dose-dense paclitaxel. It's not an unreasonable approach and it's an approach I've used in my own practice, but I've tended to use this for older women at high risk who've had comorbidities that have prevented me from using an anthracycline, for example, or for whom I was concerned about administering combination chemotherapy.

FIGURE 35

Clinical Scenario 15: *A woman has a 2.2-cm,* ***ER-positive, HER2-positive, node-positive*** *IDC (1 sentinel node).*

Which treatment would you most likely recommend for this patient, in addition to endocrine therapy, if the patient's age was:

Treatment	60 years	75 years	85 years
TCH	55%	58%	21%
AC-TH	38%	9%	1%
TC + trastuzumab	5%	18%	10%
Paclitaxel + trastuzumab	2%	9%	31%
Trastuzumab alone	0%	6%	30%
Trastuzumab + other chemotherapy	0%	0%	3%
None	0%	0%	4%

DR WINER: I don't administer trastuzumab monotherapy in the adjuvant setting because we have absolutely no data to support doing that in my mind. All of the adjuvant trials that have shown benefit with trastuzumab have been when trastuzumab has been administered either with or immediately after chemotherapy. And reasons probably exist to believe that it's better using it with rather than after chemotherapy.

For the 85-year-old woman described in Clinical Scenario 15 (Figure 35), I would argue that her risk of disease recurrence is moderate. It is by no means certain that she's going to experience recurrence. Assuming that she's entirely healthy, her chance of being alive in eight years, for example, is probably no more than 50 percent. If she were to develop recurrent disease, it's likely that it could be managed for several years with trastuzumab-based therapy.

And then, of course, you do have the option for this woman of administering endocrine therapy, which we believe still has an effect in the setting of HER2-positive disease.

I'd have to think long and hard about administering a prophylactic course of therapy to an 85-year-old. But I do believe that if I were going to administer chemotherapy and trastuzumab, this is a setting in which I would consider a regimen like paclitaxel and trastuzumab. I'd worry about the toxicity with TCH or ACTH. I believe it's a consideration.

We evaluated the paclitaxel/trastuzumab regimen in 409 patients with largely node-negative breast cancer with tumors smaller than three centimeters — mostly smaller than two centimeters. The regimen was well tolerated.

We don't have any outcome data yet, but I suspect that paclitaxel and trastuzumab will probably not be all that different from any other chemotherapy/trastuzumab combination that could be administered in the adjuvant setting.

ER status, tumor size and choice of adjuvant therapy

DR SPARANO: It's clear that patients with Stage I, HER2-positive breast cancer have a higher risk of recurrence, and the patients with ER-positive disease often would have received endocrine therapy alone.

If you're in that situation and have a HER2-positive tumor, you're then considering a recommendation not only of adjuvant chemotherapy but also of adjuvant trastuzumab.

The issues then become the tradeoffs associated with therapy. So if you have a patient who has earlier-stage disease and is older, then a greater potential for an adverse tradeoff exists because of the higher risk of cardiac toxicity and the lower absolute benefit from treatment. I believe that's what's driving the use of nonanthracycline-containing regimens, whether they be docetaxel and carboplatin or docetaxel and cyclophosphamide or, in some cases here, just paclitaxel and trastuzumab.

I believe the unanswered question would be for those patients who have small ER-positive, HER2-positive tumors: Do you need to administer chemotherapy, or would you obtain similar benefits by simply adding trastuzumab to endocrine therapy? I don't believe we have an answer to that question and, in most circumstances, patients are receiving chemotherapy in addition to trastuzumab.

I've had some situations in my own practice in which I've had patients at high risk who have ER-positive disease and are elderly. One particular patient was age 75, had a number of comorbidities, four positive nodes and ER-positive, HER2-positive breast cancer. So that's one circumstance in which I've used trastuzumab in addition to endocrine therapy without chemotherapy. I don't believe we know for sure that using trastuzumab in that way would produce the same benefit that you would obtain if you used it in combination with chemotherapy.

DR WINER: For the patient with an ER-negative, HER2-positive, 8-mm tumor, I would typically recommend some form of chemotherapy and trastuzumab. For the woman with an ER-negative, 0.3-cm tumor, I would be inclined not to, but I would probably still discuss it.

Again, my default position would be not to do it. I, again, would consider chemotherapy and trastuzumab for

FIGURE 36

Clinical Scenario 16: *A 60-year-old woman has a HER2-positive, node-negative IDC (3 sentinel nodes) and undergoes breast-conserving therapy.*

*Which adjuvant **systemic** treatment would you most likely recommend for this patient, in addition to endocrine therapy as appropriate, given the following ER status and tumor sizes?*

	ER status and tumor size			
Treatment	ER-positive		ER-negative	
	0.3-cm tumor	0.8-cm tumor	0.3-cm tumor	0.8-cm tumor
TCH	20%	56%	27%	58%
TC + trastuzumab	7%	14%	12%	15%
Paclitaxel + trastuzumab	7%	4%	5%	3%
Trastuzumab alone	6%	7%	6%	4%
AC-TH	4%	8%	8%	15%
Other	0%	1%	1%	1%
None	**56%**	**10%**	**41%**	**4%**

the 8-mm, ER-positive tumor. For the 3-mm, ER-positive tumor, I'd encourage endocrine therapy only.

We do know, at least in the short term, that women with ER-negative, HER2-negative disease experience recurrences that are earlier than women who have ER-positive, HER2-positive disease.

Care of patients with subcentimeter, HER2-positive, node-negative early BC

Breast Cancer Update
Issue 2, 2010

DR PAUL GOSS: We don't know a lot about the risk of recurrence or natural history of subcentimeter, node-negative, HER2-positive breast cancer.

Barbara Smith at Massachusetts General Hospital reported a recurrence risk rate of 10 percent over five years cumulatively, and Ana Gonzalez-Angulo and colleagues at MD Anderson recently reported a five-year recurrence risk of up to 23 percent with HER2-positive tumors of one centimeter or less (Figure 37). These patients seem to have a higher risk of recurrence than non-HER2 matched controls.

Breast Cancer Update
Issue 6, 2009

DR SPARANO: The question is, how small is too small? Is it one millimeter or two millimeters? I'm not sure about the precision of pathology for making that call, nor do I believe that we have enough data to answer that question. Dr Gonzalez-Angulo and colleagues have presented data on recurrence rates among patients with small HER2-positive tumors (Figure 37). They examined the risk of recurrence in patients with T1a or T1b node-negative breast cancer who had not received adjuvant therapy, focusing on various subgroups.

Relapse-free survival in the HER2-positive group was significantly inferior to that in the hormone receptor-positive group and the triple-negative group, so I believe some patients with smaller lesions obtain a benefit. I believe that tumor size matters, but biology also matters and probably just as much.

Breast Cancer Update
Issue 3, 2010

DR DENNIS SLAMON: Patients with subcentimeter, node-negative, HER2-positive breast cancer should receive trastuzumab-based therapy because a HER2-positive tumor is a HER2-positive tumor. The old surrogates we used are not worthless, but they were only reflections of the molecular wiring of the tumor. A HER2-positive tumor is a bad actor because HER2 activity is present even in subcentimeter tumors (Figure 37).

Breast Cancer Update
Issue 5, 2009

DR GRADISHAR: My colleagues and I share the same dilemma: How to manage small tumors. Our prior framework of thinking that small, node-negative tumors were essentially free of a risk of recurrence is being rethought. Now the whole arena has changed.

Not only do we consider ordering an Onco*type* DX assay for subcentimeter tumors, but we also consider chemotherapy. We're telling patients with small ER-positive, HER2-positive tumors that they will receive everything that we have available. We are essentially sending the message, which I believe is probably true, that biology drives the outcome.

Breast Cancer Update
Issue 6, 2008

DR MARTINE PICCART-GEBHART: Treatment of small, HER2-positive, node-negative breast cancer is a real problem in daily clinical practice. Because these patients were not allowed to enter the adjuvant trials, we have no data. I interviewed my colleagues and discovered that many do what I do, although it's based strictly on intuition.

I am offering trastuzumab to women

FIGURE 37

Prognostic role of HER2 positivity in small, node-negative breast cancer

Group	N	Patients	Main outcome
European Institute of Technology[1]	150	pT1a-b, N0	Recurrence at 5 y ER+, HER2+: 8% ER-, HER2+: 9%
MD Anderson[2]	965	pT1a-b, N0	Recurrence at 5 y HER2+: 22.9% Distant recurrence at 5 y HER2+: 13.6%
Memorial Sloan-Kettering Cancer Center[3]	257	pT1a-c, N0	Distant recurrence at 3 y No adjuvant trastuzumab: 5% Adjuvant trastuzumab: 0%

[1] Curigliano G et al. *J Clin Oncol* 2009;27(34):5693-9.
[2] Gonzalez-Angulo AM et al. *J Clin Oncol* 2009;27(34):5700-6.
[3] McArthur HL et al. Breast Cancer Symposium 2009;**Abstract 228**.

who have tumors between five millimeters and one centimeter. For tumors smaller than five millimeters, I am less comfortable with such a recommendation. Although tumor size has clear prognostic significance, I still believe the biology is bad.

You could argue that these women should receive only an anthracycline-based chemotherapy regimen. However, trastuzumab is such an elegant therapy.

DR JOHN MACKEY: For patients with these small tumors, we do not have proof of benefit from adjuvant trastuzumab. The adjuvant trastuzumab trials didn't include patients with tumors this small.

At the end of the day, we have no randomized trial evidence suggesting this would be of benefit. And, unfortunately with an effective drug such as trastuzumab, it has to be combined with chemotherapy in the adjuvant setting — at least that's the practice for which we have the evidence.

DR JULIE GRALOW: This is a tough situation because I believe trastuzumab has potential to add benefit. I don't know how much this benefit is dependent on the synergy with chemotherapy.

Within the Southwest Oncology Group, we've been talking about aromatase inhibitors with a HER2-targeted agent, at least in an ER-positive, HER2-positive setting.

We are participating in a trial evaluating paclitaxel with trastuzumab for a group of patients with node-negative disease who have otherwise good-risk features. We'll knock out the anthracycline, and weekly paclitaxel is less toxic than docetaxel/carboplatin. We struggle, however, with the question, if we're not using chemotherapy, are we providing as much benefit from trastuzumab?

If you send out for the Onco*type* DX 21-gene RS, these patients always fall in the high-risk category.

SELECT PUBLICATIONS

Baselga J et al. **First results of the NeoALTTO trial (BIG 01-06/EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S3-3**.

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Untch M et al. **Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: Results from the GeparQuattro study.** *J Clin Oncol* 2010;28(12):2024-31.

FIGURE 38

Clinical Scenario 17: *A **60-year-old woman** with a 2.2-cm, **ER-positive, HER2-positive**, node-positive IDC (1 sentinel node) receives TCH followed by trastuzumab for 1 year. After completing trastuzumab and while receiving an adjuvant AI it is discovered that the patient has bone and lung metastases that are **asymptomatic**.*

Which of the following initial treatments would you most likely recommend for this patient if the bone and lung metastases were discovered at the following points after completion of trastuzumab?

	Point after completion of trastuzumab		
Treatment	**6 months**	**18 months**	**3 years**
Lapatinib + capecitabine	30%	12%	9%
Switch endocrine therapy + lapatinib	21%	6%	2%
Trastuzumab + chemotherapy	16%	40%	41%
Switch endocrine therapy + trastuzumab	13%	28%	30%
Lapatinib + other chemotherapy	5%	3%	0%
Trastuzumab + lapatinib + chemotherapy	5%	2%	5%
Lapatinib alone	5%	3%	4%
Trastuzumab alone	3%	3%	4%
Switch endocrine therapy alone	1%	3%	5%
Other	1%	0%	0%

Anti-HER2 therapy for patients with prior adjuvant trastuzumab

DR SPARANO: My inclination would be to use trastuzumab in most circumstances. And in any of these circumstances here, whether it be six or 18 months or three years, my inclination would be to use trastuzumab in combination with chemotherapy and to reserve lapatinib.

The exception would be circumstances in which a patient experienced a recurrence while receiving adjuvant trastuzumab. That's a patient who's clearly resistant to trastuzumab, whereas for a patient whose disease recurs six months, 18 months or three years later, I'm less confident the disease is truly resistant to trastuzumab. And I wouldn't want to essentially give up that option unless I was certain we were dealing with resistant disease.

In terms of preferring trastuzumab for the patients who have experienced a relatively recent relapse, my thinking is that I'm not certain that relapse is a result of resistance to the trastuzumab. Some degree of resistance exists, but the issue in that patient may have related more to, say, resistance to the chemotherapy, which was completed much earlier, or it could have been a result of a greater occult micrometastatic disease burden.

However, if a patient experiences a recurrence while receiving adjuvant trastuzumab, I'd be confident that we're dealing with disease that's resistant to trastuzumab and that we would need to either replace that anti-HER2-directed therapy with another HER2-directed therapy — namely, lapatinib — or add a second anti-HER2-directed therapy — namely, lapatinib — to the trastuzumab backbone.

I've been using the trastuzumab/lapatinib combination predominantly for patients who've exhausted most other options. I believe it would be reasonable to consider for a patient who, for example, experienced a recurrence while receiving trastuzumab who was minimally or modestly symptomatic, with the notion that one might be able to delay the onset or the need for chemotherapy.

It's interesting that, although the response and PFS benefits were some-

FIGURE 39

Clinical Scenario 18: *A fit and otherwise healthy woman with a 2.2-cm,* ***ER-positive, HER2-positive,*** *node-positive IDC (1 sentinel node) receives TCH followed by trastuzumab for 1 year.* ***Three years after completing trastuzumab*** *and while receiving an adjuvant AI it is discovered that the patient has bone and lung metastases that are* ***asymptomatic****.*

Which of the following initial treatments would you most likely recommend if the patient's age was:

Treatment	75 years	85 years
Switch endocrine therapy + trastuzumab	35%	37%
Trastuzumab + chemotherapy	29%	13%
Lapatinib + capecitabine	15%	7%
Trastuzumab alone	7%	12%
Switch endocrine therapy + lapatinib	5%	9%
Switch endocrine therapy alone	4%	9%
Lapatinib alone	2%	8%
Trastuzumab + lapatinib	1%	4%
Other	2%	1%

what modest, a relatively greater survival benefit seemed to occur. I believe the take-home message is consistent with other studies, and that is that even in the presence of progressive disease, we obtain some value in continuing anti-HER2 therapy, whether it be using one modality targeting HER2 or two modalities targeting HER2.

DR WINER: I don't believe these are irrational answers. I believe for the patient whose disease recurs relatively soon after trastuzumab, switching to another anti-HER2 agent is appealing, so that's where lapatinib/capecitabine comes in. But in much the same way that we often take a patient from one trastuzumab/chemotherapy regimen to another, this is someone who has essentially experienced disease progression within six months — who's experienced disease progression on first-line therapy. You're moving on to second-line therapy, and that second-line therapy could be chemotherapy in combination with trastuzumab.

For the patient whose disease recurred early on, I would probably administer lapatinib and capecitabine, and in the other situations, I'd probably retry trastuzumab.

I was struck by the data from the trial that was led by Joyce O'Shaughnessy and Kim Blackwell that was published in the *JCO* earlier this year showing a survival advantage for trastuzumab/lapatinib in patients with highly refractory disease compared to lapatinib alone.

I believe something is a little special about the combination. I realize you asked me about nontrial use, but we've had trials administering this in both first- and second-line settings, which at least on an anecdotal basis have been encouraging.

I believe that this is a combination that has legs. And it's one that I occasionally use outside of a trial not only for patients with fairly refractory disease, but also sometimes for patients with earlier-stage disease, in whom I want to avoid the side effects with chemotherapy.

Breast Cancer Update *Think Tank*
Issue 1, 2011

DR HAROLD BURSTEIN: Clearly we have seen that patients can respond to multiple lines of anti-HER2 treatment, and it's been difficult to prove that any of the treatments is significantly different from any other treatment, and the sequencing probably doesn't matter much. When treatments work in oncology, we can "mine that vein" deeply.

HER2-targeted therapy really works. We can use small-molecule tyrosine kinase inhibitors, targeted vehicles for delivering chemotherapy and other antibodies. In the grand scheme, the question of how to integrate our treatments will require more clinical data to answer.

Breast Cancer Update *Think Tank*
Issue 1, 2011

DR ANTONIO WOLFF: One of the important questions we had from the beginning was how long to continue anti-HER2 therapy at the time of disease progression for patients with metastatic breast cancer. Increasingly, I believe the answer is that patients should continue to receive some type of anti-HER2 therapy. It is not clear to me that any anti-HER2 therapy is necessarily better than another one.

For many patients whom I start on first-line trastuzumab, I tend to switch chemotherapy and maintain the patient on various trastuzumab/chemotherapy combinations for a while. The question is whether we should be considering the use of combination anti-HER2 therapy based on the data with lapatinib/trastuzumab.

Breast Cancer Update
Issue 1, 2011

DR GIANNI: In terms of treating metastatic disease after prior chemotherapy/trastuzumab, this is a completely new

FIGURE 40

Clinical Scenario 19: *A **60-year-old** woman with a 2.2-cm, **ER-positive, HER2-positive**, node-positive IDC (1 sentinel node) receives TCH followed by trastuzumab for 1 year. After completing trastuzumab and while receiving an adjuvant AI it is discovered that the patient has bone and lung metastases that are **very symptomatic** (pain and dyspnea).*

Which of the following initial treatments would you most likely recommend for this patient if the bone and lung metastases were discovered at the following points after completion of trastuzumab?

	Point after completion of trastuzumab		
Treatment	**6 months**	**18 months**	**3 years**
Lapatinib + capecitabine	47%	18%	10%
Trastuzumab + chemotherapy	27%	68%	70%
Lapatinib + other chemotherapy	11%	3%	3%
Trastuzumab + lapatinib + chemotherapy	5%	5%	6%
Trastuzumab alone	3%	2%	3%
Lapatinib alone	3%	1%	1%
Switch endocrine therapy + trastuzumab	0%	3%	7%
Other	4%	0%	0%

field. Nobody has a reasonable answer about how to choose treatments for these patients. We have no idea whether these relapses are resistant relapses or relapses due to the fact that duration of treatment was inadequate or that the relapsed disease is less sensitive to rechallenging with anti-HER2 therapy.

In practice we rechallenge these patients with HER2-directed treatment. Whether this is the best approach and whether this is a subgroup of women who indeed have developed resistance, we still do not know. In a way, it's good that we do not know because the introduction of trastuzumab into therapy was so efficacious that we don't have enough of these patients experiencing relapse to tell us this story.

Typically I use trastuzumab. In Europe, lapatinib cannot be used at first relapse, nor can it be combined with trastuzumab. If I had an option, I would try combining trastuzumab and whatever gentle therapy I could use, including either lapatinib or bevacizumab. We shouldn't forget that bevacizumab has the ability to dramatically increase the activity of trastuzumab, and the NSABP and CIRG have completed a trial testing the approach of combining bevacizumab and trastuzumab. We are eagerly awaiting the results of that trial.

Two trials in metastatic breast cancer have completed accrual and have the potential to redefine this scenario. First, a study is evaluating trastuzumab and docetaxel, combined with either placebo or bevacizumab, and in the CLEOPATRA study, docetaxel and trastuzumab is combined with pertuzumab or placebo.

Both trials have been conducted as first-line treatment for HER2-positive metastatic breast cancer, and a fraction of the patients have already been exposed to trastuzumab during adjuvant treatment. The results of that subset will help us to understand what's going on in these cases.

Breast Cancer Update
Issue 1, 2011

DR ROBERT: I probably have a lower threshold for using lapatinib earlier for patients whose disease recurrs after prior treatment with trastuzumab.

For patients with a disease-free interval of at least one year, I would consider using trastuzumab with vinorelbine. That combination is an effective regimen and is well tolerated. We have a number of options for these patients, including combining trastuzumab with taxanes, capecitabine, gemcitabine or pegylated anthracyclines. Of course, we also have capecitabine with lapatinib or trastuzumab with lapatinib.

Combination of hormonal and anti-HER2 therapy

Breast Cancer Update
Issue 5, 2009

DR GRADISHAR: The data evaluating the combination of AIs with anti-HER2 agents from the TAnDEM study and

FIGURE 41

Clinical Scenario 20: *A fit and otherwise healthy woman with a 2.2-cm,* ***ER-positive, HER2-positive****, node-positive IDC (1 sentinel node) receives TCH followed by trastuzumab for 1 year.* ***Three years after completing trastuzumab*** *and while receiving an adjuvant AI it is discovered that the patient has bone and lung metastases that are* ***very symptomatic*** *(pain and dyspnea).*

Which treatment would you most likely recommend for this patient, in addition to endocrine therapy, if the patient's age was:

Treatment	75 years	85 years
Trastuzumab + chemotherapy	56%	34%
Lapatinib + capecitabine	17%	12%
Switch endocrine therapy + trastuzumab	8%	17%
Trastuzumab alone	6%	15%
Trastuzumab + lapatinib + chemotherapy	4%	1%
Trastuzumab + lapatinib	3%	3%
Switch endocrine therapy + lapatinib	2%	8%
Lapatinib alone	2%	8%
Other	2%	2%

FIGURE 42

Combined aromatase inhibitor and HER2-targeted treatments for postmenopausal patients with HER2-positive, ER-positive metastatic breast cancer

	TAnDEM			EGF30008		
	Anastrozole + trastuzumab	Anastrozole	*p*-value	Letrozole + lapatinib	Letrozole	*p*-value
Median PFS	4.8 mo	2.4 mo	0.0016	8.2 mo	3.0 mo	0.019
Median OS	28.5 mo	23.9 mo	0.325	33.3 mo	32.3 mo	0.113
CBR	42.7%	27.9%	0.026	48%	29%	0.003

PFS = progression-free survival; OS = overall survival; CBR = objective response + stable disease

Johnston S et al. San Antonio Breast Cancer Symposium 2008;**Abstract 46**; Mackey JR et al. San Antonio Breast Cancer Symposium 2006. No abstract available

from the EGF30008 trial are concordant. Patients with ER-positive, HER2-positive tumors have tended to fare poorly with AI therapy alone. Both of these trials showed PFS periods of several months with AI therapy alone, but the outcomes were incrementally improved when the anti-HER2 agent was added (Figure 42). You are obtaining an effect by leveraging two different pathways.

Breast Cancer Update
Issue 3, 2009

DR MICHAEL PRESS: The study of letrozole with lapatinib versus letrozole alone for patients with ER-positive, HER2-positive metastatic breast cancer suggests cross talk between the growth factor and steroid receptor pathways such that when HER2 is activated through amplification and overexpression, it activates the estrogen receptor pathway, either directly or indirectly. The data suggest that the best therapy for those patients would be an agent that interacts with and interferes with both the HER2 pathway and the estrogen receptor pathway.

Breast Cancer Update
Issue 1, 2009

DR MARK PEGRAM: The EGF30008 trial was conducted in a patient population not selected for HER2 status, but it was statistically powered to evaluate the subset with HER2-positive disease as the primary endpoint.

In fact, the statistical plan called for the analysis of that subset first, and only if that reached statistical significance would they analyze the intent-to-treat population, which included all of the patients with HER2-negative disease.

The result was a statistically significant increase in PFS and response rate with lapatinib/letrozole compared to letrozole alone among patients with ER/PR-positive, HER2-positive disease. The overall survival data are immature, with an interesting trend that did not reach statistical significance — a longer data-capture period is required.

As the results were positive for patients with HER2-positive disease,

FIGURE 43

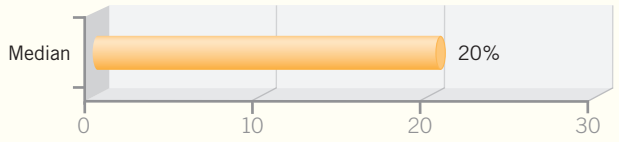
Clinical Scenario 21: *A* ***60-year-old*** *woman with a 2.2-cm,* ***ER-negative, HER2-positive****, node-positive IDC (1 sentinel node) receives TCH followed by trastuzumab for 1 year.* ***Eighteen months after completing trastuzumab*** *it is discovered that the patient has bone and lung metastases.*

Which treatment would you most likely recommend if the patient was:

Treatment	Asymptomatic	Very symptomatic with pain and dyspnea
Trastuzumab + chemotherapy	55%	60%
Lapatinib + capecitabine	20%	18%
Trastuzumab alone	9%	1%
Lapatinib alone	8%	4%
Trastuzumab + lapatinib	3%	0%
Trastuzumab + lapatinib + chemotherapy	3%	11%
Lapatinib + other chemotherapy	2%	6%

FIGURE 44

Approximately what percent of your patients with HER2-positive metastatic disease develop brain metastases at some point in the course of their disease?



Have you observed any patients with HER2-positive brain metastases who experienced an objective CNS tumor response to systemic anti-HER2 treatment?

they studied the entire cohort of 1,286 subjects, most of whom had ER/PR-positive, HER2-negative disease. In the group with HER2-negative disease, no efficacy signal was noted.

Another interesting twist in the statistical plan stipulated evaluating those patients who experienced disease progression within six months of discontinuing adjuvant tamoxifen. In that group, which by protocol definition was an endocrine-resistant subpopulation of the patients with HER2-negative disease, a statistically nonsignificant increase in PFS was observed with lapatinib/letrozole.

This raises the possibility that something of note might be occurring in endocrine-resistant, HER2-negative disease, which would require confirmation in prospective randomized trials. It's not practice changing in this population at this point. But the primary endpoint of the study in HER2-positive disease might be practice changing.

It offers an appealing, perhaps therapeutic, option for patients with ER-positive, HER2-positive metastatic disease. Now you can consider targeting HER2 and ER with an oral-only regimen.

CNS tumor response to anti-HER2 therapy

DR WINER: I've definitely seen a CNS tumor response with the combination of capecitabine and lapatinib. And I've also seen it with some trastuzumab combinations, but in those situations it may be just the chemotherapy you're combining with trastuzumab that's leading to that response. We know that chemotherapy to some degree gets into the brain and can lead to objective responses.

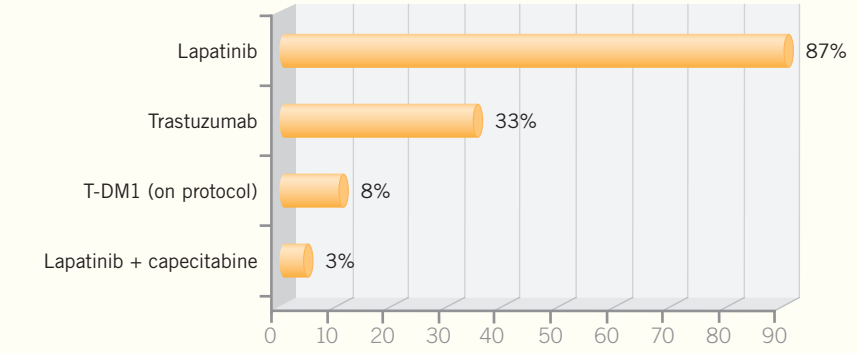
Breast Cancer Update
Issue 5, 2008

DR JOYCE O'SHAUGHNESSY: Capecitabine/lapatinib is an important combination, particularly for patients who have or are at high risk for developing brain metastases. At ASCO 2008, Dr Boccardo reported an 18 percent objective response rate among patients who had definitive progressing brain metastases at the time of study entry.

These data corroborated Lin and Winer's experience presented at the San Antonio Breast Cancer Symposium in 2007. The responses are impressive. Brain metastases are a scourge, and we have little to offer these patients other than radiation therapy. Thus I am "bullish" on the capecitabine/lapatinib regimen as our most promising strategy to help these patients, and I like to use it earlier in the metastatic setting.

FIGURE 45

With which of the following agents have you observed an objective CNS tumor response to systemic anti-HER2 treatment? (May have more than 1 response)



n = 39

FIGURE 46

Clinical Scenario 22: *A woman with a 2.2-cm,* ***ER-negative, HER2-positive,*** *node-positive IDC (1 sentinel node) receives TCH followed by trastuzumab for 1 year.* ***Eighteen months after completing trastuzumab*** *it is discovered that the patient has bone and lung metastases that are* ***asymptomatic. The patient receives capecitabine and trastuzumab and has stable disease for 4 months, after which the disease progresses but no new sites of disease are evident and the patient is still asymptomatic.***

Which treatment would you most likely recommend if the patient's age was:

Treatment	60 years	75 years	85 years
Trastuzumab + chemotherapy	40%	35%	22%
Lapatinib + other chemotherapy	22%	20%	11%
Lapatinib + capecitabine	19%	19%	12%
Trastuzumab + lapatinib	7%	13%	17%
Trastuzumab + lapatinib + chemotherapy	6%	1%	0%
Lapatinib alone	4%	11%	29%
Trastuzumab alone	2%	1%	9%

Breast Cancer Update
Issue 2, 2009

DR IAN KROP: CNS metastases develop in approximately 30 to 40 percent of patients with advanced HER2-positive breast cancer. It's possible that by using a small molecule such as lapatinib we may be able to have an effect on this site of disease. Nancy Lin and colleagues at Dana-Farber initiated a small study of single-agent lapatinib for patients who had CNS metastases from HER2-positive breast cancer that progressed despite palliative radiation therapy.

We do not have many options for those patients. She observed a small but significant rate of CNS responses. The study was expanded to combine lapatinib with capecitabine, and again, a small but significant number of patients benefited. So currently she's evaluating the combination of other chemotherapeutic agents, including epothilones, with lapatinib for patients with CNS metastases.

Continuation of trastuzumab after disease progression

Breast Cancer Update
Issue 2, 2010

DR GOSS: The synergistic interaction of lapatinib combined with trastuzumab has been established in HER2-positive preclinical models. Clinical trial data are also available showing the efficacy and safety of this combination.

A randomized Phase II study showed improved efficacy with lapatinib/trastuzumab compared to lapatinib alone in heavily pretreated HER2-positive metastatic breast cancer progressing on trastuzumab. Updated data on overall survival were recently reported and showed a significantly improved overall survival (Figure 50).

The activity of the combination is extremely interesting, especially because these patients no longer seem to benefit from either agent alone. I believe these data are important because time to mortality is profoundly shortened in this subset of patients with HER2-positive breast cancer.

Breast Cancer Update
Issue 4, 2010

DR GEYER: A study recently reported on women with disease refractory to trastuzumab who were randomly assigned to full-dose lapatinib versus an attenuated dose of lapatinib with continued trastuzumab. The design of that

FIGURE 47

Clinical Scenario 23: *A woman with a 2.2-cm,* ***ER-negative, HER2-positive****, node-positive IDC (1 sentinel node) receives TCH followed by trastuzumab for 1 year.* ***Eighteen months after completing trastuzumab*** *it is discovered that the patient has bone and lung metastases that are asymptomatic. The patient receives capecitabine and trastuzumab and has stable disease for 4 months, after which the disease progresses but no new sites of disease are evident and the patient is still asymptomatic.* ***The patient receives trastuzumab/vinorelbine and experiences a minor response that lasts 9 months but then develops disease progression in the same sites and experiences moderate symptoms (bone pain, asthenia).***

Which treatment would you most likely recommend if the patient's age was:

Treatment	60 years	75 years	85 years
Lapatinib + capecitabine	27%	26%	18%
Lapatinib + other chemotherapy	27%	23%	12%
Trastuzumab + chemotherapy	16%	12%	7%
Trastuzumab + lapatinib + chemotherapy	13%	9%	4%
Trastuzumab + lapatinib	11%	17%	22%
Lapatinib alone	3%	11%	29%
Trastuzumab alone	2%	1%	6%
Other	1%	1%	2%

FIGURE 48

A Phase III randomized comparison of lapatinib (L) with capecitabine (C) versus capecitabine alone for women with advanced breast cancer that has progressed on trastuzumab

	C (n = 201)	C + L (n = 198)	Hazard ratio	*p*-value
Median TTP	18.6 wk	27.1 wk	0.57	<0.001
Median OS	66.6 wk	67.7 wk	0.78	0.177

TTP = time to progression; OS = overall survival

Cameron D et al. *Breast Cancer Res Treat* 2008;112(3):533-43.

study appears as if the deck is stacked in favor of lapatinib.

Remarkably, however, in this population with heavily pretreated advanced breast cancer, the combination resulted in an improvement in PFS and a survival advantage (Figure 50). This has greatly affected how I practice. I find myself using trastuzumab/lapatinib to give patients some time off chemotherapy.

Breast Cancer Update
Issue 1, 2010

PROF UNTCH: In the von Minckwitz study, eligible patients who previously received chemotherapy and trastuzumab and were not responding or experienced recurrence were randomly assigned to trastuzumab in combination with capecitabine versus capecitabine alone.

The combination of trastuzumab/capecitabine was better than capecitabine alone in terms of time to disease progression — 8.2 months compared to 5.6 months, with a hazard ratio of 0.69 (Figure 49). The proof of principle was that, yes, treatment beyond disease progression is beneficial.

The trial was stopped prematurely when the data from the capecitabine/lapatinib study became available (Figure 48). Similar results were observed with the combination of lapatinib and trastuzumab for patients with heavily pretreated metastatic breast cancer and disease progression during trastuzumab treatment.

T-DM1 for HER2-positive BC

DR WINER: At ESMO 2010, a randomized Phase II trial comparing docetaxel/trastuzumab to trastuzumab-DM1 (T-DM1) was presented. The follow-up was short. No data were presented in terms of time to progression.

Response rates were comparable between the two arms but were numerically slightly higher in the T-DM1 arm. The big difference was toxicity, which was dramatically reduced with T-DM1 versus docetaxel/trastuzumab. Compared to docetaxel/trastuzumab, the toxicity with T-DM1 was minimal.

I absolutely would administer T-DM1 if it were available off protocol. I've used it a great deal in the context of clinical trials. It is an incredibly well-tolerated drug that, for patients who have received fairly extensive prior anti-HER2 therapy, is still remarkably effective. And I would use it in either a first-line or a second-line

FIGURE 49

Trastuzumab beyond progression in HER2-positive advanced breast cancer: A German Breast Group 26/Breast International Group 03-05 study of capecitabine (C) with or without trastuzumab (H)

	C (n = 78)	C + H (n = 78)	Hazard ratio	*p*-value
Median TTP	5.64 mo	8.16 mo	0.685	0.0338
Median OS	20.39 mo	25.48 mo	0.763	0.2570

TTP = time to progression; OS = overall survival

Von Minckwitz G et al. *J Clin Oncol* 2009;27(12):1999-2006.

FIGURE 50

EGF104900: A randomized Phase III study of lapatinib (L) versus lapatinib with trastuzumab (T) for patients with HER2-positive, trastuzumab-refractory metastatic breast cancer

	L (n = 145)	L + T (n = 146)	Hazard ratio	*p*-value
Median PFS	8.1 wk	12.0 wk	0.73	0.008
Median OS	9.5 mo	14 mo	0.74	0.026

PFS = progression-free survival; OS = overall survival
Median number of prior trastuzumab regimens for metastatic breast cancer: 3

"This study demonstrated that lapatinib in combination with trastuzumab offers a chemotherapy-free option that has an acceptable tolerability profile and, versus lapatinib alone, reduced the risk of disease progression by 27% (P = .008). The efficacy benefits arose in a treatment setting that lacked many of the well-known chemotherapy-related toxicities."

Blackwell KL et al. *J Clin Oncol* 2010;28(7):1124-30; Blackwell KL et al. San Antonio Breast Cancer Symposium 2009;**Abstract 61**.

situation, if I had that ability. If it were only approved as a later-line therapy, I would use it in that setting and reserve my earlier use for clinical trials.

Breast Cancer Update *Think Tank* Issue 1, 2011

DR BURSTEIN: T-DM1 is a conjugate in which trastuzumab has been chemically linked to the chemotherapy moiety, DM1, which is an old maytansinoid chemotherapy that NCI had in the 1970s. They've been able to link three or four molecules of that to trastuzumab and deliver it as a targeted drug.

Interestingly, people are calling it non-chemotherapy because it doesn't have the side effects of chemotherapy. It doesn't make patients nauseated. It doesn't lower their blood counts in dramatic ways. It doesn't make their hair fall out.

T-DM1 has been studied in both Phase I and now a couple of Phase II studies for patients with multirefractory HER2-positive disease, including a study with about 100 patients who had received an anthracycline, taxanes, trastuzumab, capecitabine and lapatinib, and it clearly causes robust responses of about 30 to 40 percent in that patient population (Figure 52).

We've done a lot of the Phase I work, and it seems like a terrific drug. The responses we see are robust in patients who have received a lot of prior therapy. The side effects are associated with chronic exposure and include fatigue and some thrombocytopenia without major clinical sequelae.

T-DM1 is administered every three weeks, and it appears to be quite impressive. It's obviously one of the several pipeline drugs for HER2-positive disease, but if I had to handicap the field, I would give this one a high score.

Breast Cancer Update *Think Tank* Issue 1, 2011

DR SWAIN: T-DM1 is trastuzumab at a much lower dose linked to maytansine. Maytansine is an older drug that was associated with a lot of toxicity many years ago, so it wasn't developed further. In a study with over 100 patients who had heavily pretreated disease, the response rate with T-DM1 was 34 percent, which is an exciting result for a group of patients with such heavily pretreated disease (Figure 52). So I believe that it's certainly the "hottest" drug right now, besides pertuzumab, for HER2-targeted therapy.

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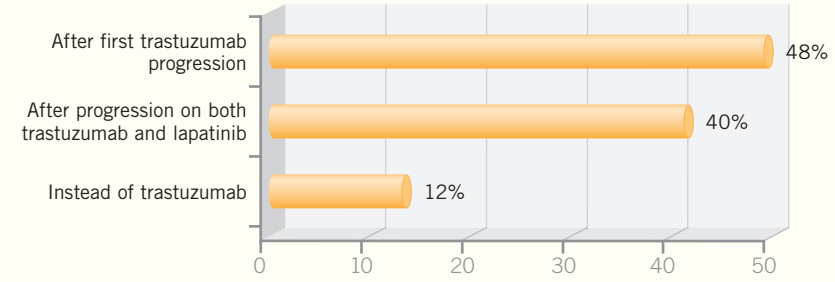
FIGURE 51

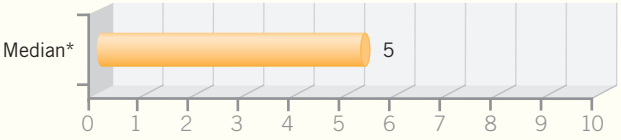
Are you familiar with the agent T-DM1?

If T-DM1 were available off protocol, how would you use it?



n = 67

To how many of your current patients would you offer T-DM1 if it were available?



* Excludes 18 respondents who answered "I don't know"

n = 67

FIGURE 52

Phase II trial of T-DM1 for patients with HER2-positive metastatic breast cancer who experienced disease progression on prior HER2-directed therapy

	Investigator		Independent review	
	All (N = 112)	HER2 centrally confirmed (N = 74)	All (N = 112)	HER2 centrally confirmed (N = 74)
Overall response rate	37.5%	47.3%	25.9%	33.8%
Clinical benefit rate (CBR)*	76.8%	NR	75%	NR

* CBR = complete response + partial response + stable disease ≥ 6 months; NR = not reported

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How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Results of the FIRST trial comparing front-line anastrozole to high-dose fulvestrant	4 3 2 1	4 3 2 1
Postadjuvant trastuzumab disease-free interval and selection of further anti-HER2 treatment	4 3 2 1	4 3 2 1
Practical role of BRCA mutation testing for older patients with TNBC	4 3 2 1	4 3 2 1
Mechanism of action of T-DM1	4 3 2 1	4 3 2 1
Clinical activity of ixabepilone in the TNBC subset	4 3 2 1	4 3 2 1
Practical impact of Onco*type* DX RS values on chemotherapy regimen selection	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

AS A RESULT OF THIS ACTIVITY, I WILL BE ABLE TO:

- Compare and contrast management strategies employed by community-based medical oncologists and clinical investigators in the treatment of breast cancer, and use this information to refine or validate practical treatment decision-making. ..... 4 3 2 1 N/M N/A
- Identify clinical scenarios for which relative agreement and heterogeneity exist in patterns of breast cancer care, and apply these findings to the individualized care of patients. ..... 4 3 2 1 N/M N/A
- Counsel patients with breast cancer about the benefits and risks of multiple acceptable evidence-based treatment options when they exist. ..... 4 3 2 1 N/M N/A
- Apply the results of new data with biomarkers and multigene assays to the routine care of patients with breast cancer. ..... 4 3 2 1 N/M N/A
- Explain to patients how breast cancer molecular subtype influences disease prognosis and selection of appropriate systemic treatment. ..... 4 3 2 1 N/M N/A
- Recognize the rate at which practice-changing clinical research influences oncologist behavior, and explain how this affects patient access to standard and novel therapeutics. ..... 4 3 2 1 N/M N/A
- Recall the design and eligibility criteria for ongoing breast cancer clinical trials, and consent or refer appropriate patients for study participation. ..... 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities: .....

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty for this educational activity

To what extent do you feel the faculty members' comments were helpful or not helpful?

Please be as specific as possible about individual faculty.

.....

.....

Please recommend additional faculty for future activities:

.....

.....

Other comments about the faculty for this activity:

.....

.....

REQUEST FOR CREDIT — Please print clearly

Name:..... Specialty:.....

Professional Designation:

☐ MD ☐ PharmD ☐ NP

☐ DO ☐ RN ☐ PA ☐ Other.....

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City, State, Zip:.....

Telephone:..... Fax:.....

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature:..... Date:.....

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Patterns of Care in Medical Oncology

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